A CROSS SECTIONAL STUDY TO ASSESS OLFACTORY FUNCTION AND QUALITY OF LIFE CHANGES IN PATIENTS WITH ALLERGIC RHINITIS BEFORE AND AFTER MEDICAL THERAPY

A dissertation submitted to the Tamil Nadu Dr. M. G. R. Medical University, Chennai in partial fulfilment of the requirement for the MS Otorhinolaryngology (Branch IV) degree examination to be held in April 2017.

A CROSS SECTIONAL STUDY TO ASSESS OLFACTORY FUNCTION AND QUALITY OF LIFE CHANGES IN PATIENTS WITH ALLERGIC RHINITIS BEFORE AND AFTER MEDICAL THERAPY

Dissertation submitted to the

THE TAMIL NADU DR. MGR MEDICAL UNIVERSITY, CHENNAI

In partial fulfilment of the requirements for the degree of

MASTER OF SURGERY

IN

OTORHINOLARYNGOLOGY

By

KATTI BLESSI SARA

Register number: 221414353

DEPARTMENT OF OTORHINOLARYNGOLOGY

CHRISTIAN MEDICAL COLLEGE

VELLORE

APRIL 2017

CERTIFICATE

This is to certify that "**A CROSS SECTIONAL STUDY TO ASSESS OLFACTORY FUNCTION AND QUALITY OF LIFE CHANGES IN PATIENTS WITH ALLERGIC RHINITIS BEFORE AND AFTER MEDICAL THERAPY**" is the bonafide work of Dr. KattiBlessi Sara under my supervision in the Department of Otorhinolaryngology, Christian Medical College Vellore in partial fulfilment of the requirements for the M.S ENT Examination Branch IV of the Tamil Nadu Dr. M.G.R Medial University to be held in April 2017 and no part thereof has been submitted for any other degree.

Dr. Rupa VedantamMS,DLO

Professor and Head

Department of ENT Unit 3

Christian Medical College&Hospital

Vellore-632004.

India

CERTIFICATE BY THE HEAD OF THE DEPARTMENT/ PRINCIPAL

This to certify that "**A CROSS SECTIONAL STUDY TO ASSESS OLFACTORY FUNCTION AND QUALITY OF LIFE CHANGES IN PATIENTS WITH ALLERGIC RHINITIS BEFORE AND AFTER MEDICAL THERAPY"** is the bonafide work of Dr.KattiBlessi Sara under the supervision of Dr.RupaVedantam, Professor and head of ENT unit 3 in the Department of ENT, Christian Medical College Vellore.

Dr.Rita Ruby AnbuselviDr Anna P Pulimood

Professor and Head, Principal

Department of Otorhinolaryngology,Christian Medical College

Christian Medical CollegeVellore.

Vellore.

DECLARATION

I, Katti Blessi Sara, do hereby declare that the dissertation titled "**A CROSS SECTIONAL STUDY TO ASSESS OLFACTORY FUNCTION AND QUALITY OF LIFE CHANGES IN PATIENTS WITH ALLERGIC RHINITIS BEFORE AND AFTER MEDICAL THERAPY"** is a genuine record of research done by me under the supervision and guidance of Dr Rupa Vedantam, Professor and head, Department of ENT-Unit 3, Christian Medical College, Vellore and has not previously formed the basis of award of any degree, diploma, fellowship or other similar title of any university or institution.

Vellore Katti Blessi Sara

Date

Acknowledgements

I would like to thank God for giving me this opportunity to study and His divine providence in helping me to finish this dissertation.

I would like to express my deep gratitude to my esteemed guide and teacher, Professor and head, Dr. Rupa Vedantam for designing the study, for her constant support, meticulous guidance without which this dissertation would not have been possible.

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Lastly, I am so thankful to God for my parents, younger brother and younger sister Esther, for all the technical help and fine tuning my work and continuously cheering me to accomplish what I am assigned with.

Introduction

Chemosensation, which includes the sensations of both smell and taste, is an important aspect of the sensory system in human beings. It involves the transduction of chemicals into sensations. Olfaction is the special sense mediated by sensory cells 45 located in the olfactory area of the nasal cavity. One of the prime uses of the sense of olfaction in human beings is that it is helps to act as a surveillance system which detects the hazards in the environment. The other functions of the olfactory system include 57 generating feelings of pleasure, promoting adequate nutrition, influencing sexuality and influencing mood. Any cause of dysfunction could potentially be a source of emotional distress to the patient(2).

The sensation of olfaction may be affected by various physiological and pathological conditions. Some of the physiological conditions that can affect the sensation of smell include age, puberty and pregnancy. A decreased sense of smell may

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Additional Vice Principal (Research)

November 16, 2014

Dr. Katti Blessi Sara
PG Registrar
Department of ENT
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Sub: **Fluid Research Grant Project:**
Study of olfactory disturbances and quality of life in patients with allergic rhinitis and the reversal of these parameters after medical therapy in affected patients.
Dr. Katti Blessi Sara, Dr. Rupa Vedantam, ENT, Ms. Tanny Sebastian, Biostatistics, Dr. Vijay Kumar Lukka, Dr. Raghav Mohan, Dr. John Mathew, ENT, CMC, Vellore.

Ref: IRB Min No: 9094 [OBS-(RVE)] dated 06.10.2014

Dear Dr. Katti Blessi Sara,

I enclose the following documents:

1. Institutional Review Board approval letter
2. Agreement

Could you please sign the agreement and send it to Dr. Nihal Thomas, Addl. Vice Principal (Research), so that the grant money can be released.

With best wishes,

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

Dr. NIHAL THOMAS
M.D., M.N.A.M.S., D.N.B.(Endo), F.R.A.C.P.(Endo), F.R.C.P.(Edin), F.R.C.P.(Glasg)
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Christian Medical College, Vellore - 632 002.

Cc. Dr. Rupa Vedantam, ENT, CMC, Vellore.

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Dr. Vijay Kumar Lukka, Dr. Raghav Mehra, Dr. John Mathew, ENT, CMC, Vellore.

Ref: IRB Min No. 9094 [OBSERVE] dated 08.10.2014

Dear Dr. Katti Blessi Sara,

The Institutional Review Board (Blue, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project entitled "Study of olfactory disturbances and quality of life in patients with allergic rhinitis and the reversal of these parameters after medical therapy in affected patients." on October 6th 2014.

The Committees reviewed the following documents:

1. IRB Application format
2. Proforma
3. Questionnaire (English)
4. Information Sheet and Informed Consent Form (English, Tamil, Hindi, Telugu)
5. Cvs of Drs. Katti Blessi Sara, Vijay Kumar Lukka, John Mathew, Rupa Vedantam , Ms. Tunny Sebastian
6. No of documents 1-5

The following Institutional Review Board (Blue, Research & Ethics Committee) members were present at the meeting held on October 6th 2014 in the CREST/SACN Conference Room, Christian Medical College, Bagayam, Vellore 632002.

Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

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Deputy Chairperson
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Name	Qualification	Designation	Other Affiliations
Dr. Chandra Singh	MS, MCH, DMB	Professor, Urology, CMC.	Internal, Clinician
Dr. Vivek Mathew	MD (Gen. Med.) D.M (Neuro) Dip. NB (Neuro)	Professor, Neurology, CMC, Vellore	Internal, Clinician
Dr. Simon Pavamani	MBBS, MD,	Professor, Radiotherapy, CMC, Vellore	Internal, Clinician
Dr. Niranjan Thomas	DCH, MD, DNB (Paediatrics)	Professor, Neonatology, CMC, Vellore	Internal, Clinician
Dr. Mathew Joseph	MBBS, MCH	Professor, Neurosurgery, CMC, Vellore	Internal, Clinician
Dr. Visalakshi. J	MPM, PhD	Lecturer, Dept of Biostatistics, CMC, Vellore	Internal, Statistician
Dr. Jacob John	MBBS, MD	Associate Professor, Community Health, CMC, Vellore	Internal, Clinician
Dr. T. Balamugesh	MBBS, MD(Int Med), DM, FCCP (USA)	Professor, Pulmonary Medicine, CMC, Vellore	Internal, Clinician
Dr. B. J. Prashantham	MA(Counseling Psychology), MA(Theology), Dr. Min(Clinical Counselling)	Chairperson, Ethics Committee, IRB. Director, Christian Counseling Centre, Vellore	External, Social Scientist
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We approve the project to be conducted as presented.

The Institutional Ethics Committee expects to be informed about the progress of the project, any **adverse events** occurring in the course of the project, any **amendments in the protocol and the patient information / informed consent**. On completion of the study you are expected to submit a copy of the **final report**. Respective forms can be downloaded from the following link: http://172.16.11.136/Research/IRB_Polices.html in the CMC Intranet and in the CMC website link address: http://www.cmch-vellore.edu/static/research/Index.html

Fund Grant Allocation:

A sum of 98,125/- INR (Rupee Ninety Eight Thousand One Hundred and Twenty Five only) will be granted for Two years.

Yours sincerely

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

Dr. NIHAL THOMAS
SECRETARY - (ETHICS COMMITTEE)
Institutional Review Board,
Christian Medical College, Vellore - 632 002.

Cc. Dr. Rupa Vedantam, ENT, CMC, Vellore.

ABSTRACT

TITLE

A cross sectional study to assess olfactory function and quality of life changes in patients with allergic rhinitis before and after medical therapy.

.

DEPARTMENT

Department of Otorhinolaryngology, Christian Medical College, Vellore

NAME OF THE CANDIDATE :KattiBlessi Sara

DEGREE AND SUBJECT : MS ENT

NAME OF THE GUIDE :Dr Rupa Vedantam

BACKGROUND

Allergic rhinitis is a common inflammatory disease prevalent world wide which is known to affect both olfaction and quality of life. Very little information is available regarding the impact of medical therapy on these parameters in patient with allergic rhinitis in the Indian subcontinent.

OBJECTIVES

1)To assess the prevalence of olfactory dysfunction in patients diagnosed with allergic rhinitis

2) To evaluate associated quality- of –life changes in patients diagnosed with allergic rhinitis 3) To assess the reversal of olfactory dysfunction and any change in quality –of-life in affected patients following medical therapy

METHODS

A cross-sectionalhospital based study was conducted prospectively in patients diagnosed with allergic rhinitis All recruited patients underwent butanol threshold testing for assessment of olfactory function and assessment of quality of life using a RQLQ questionnaire. These patients underwent medical therapy with steroidal nasal spray, antihistamines and/ or leukotriene receptor antagonists for about 8-12 weeks

At the end of therapy, the same tests were administered again. As there is no normative data for the Indian population, 40 normal individuals were tested to obtain normative data for olfaction testing.

RESULTS

A total of 150 patients with allergic rhinitis were recruited. Most patients (72%) had intermittent, mild or moderate allergic rhinitis. Smokers were more likely to have moderate to severe allergic rhinitis than non-smokers ($p=0.01$). The prevalence of hyposmia in patients with allergic rhinitis was 28.7%. The degree of hyposmia was mild (52.9%) or moderate (35.3%)in the majority. Following therapy, there was a significant improvement in olfaction scores ($p=0.001$). Quality of life (QOL)was affected in all patients with allergic rhinitis and the mean QOL scores were raised, particularly those affecting nasal, emotional and non-nasal symptoms. These scores also showed a

significant improvement following therapy (p=0.00)

CONCLUSION

Allergic rhinitis impacts both olfaction and quality of life in Indian patients. The problem is more pronounced in smokers. With adequate medical therapy which includes a steroid nasal spray, antihistamine and leukotriene anatagonist, most patients find significant benefit both for olfaction as well as quality of life.

Contents

Introduction

Chemosensation, which includes the sensations of both smell and taste, is an important aspect of the sensory system in human beings. It involves the transduction of chemicals into sensations. Olfaction is the special sense mediated by sensory cells located in the olfactory area of the nasal cavity. One of the prime uses of the sense of olfaction in human beings is that it is helps to act as a surveillance system which detects the hazards in the environment. The other functions of the olfactory system include generating feelings of pleasure, promoting adequate nutrition, influencing sexuality and influencing mood. Any cause of dysfunction could potentially be a source of emotional distress to the patient(2).

The sensation of olfaction may be affected by various physiological and pathological conditions. Some of the physiological conditions that can affect the sensation of smell include age, puberty and pregnancy. A decreased sense of smell may be associated with certain nasal conditions like allergic rhinitis, atrophic rhinitis and sinonasal polyposis. Head trauma can sever the olfactory rootlets and cause anosmia. Tumours of the nasal cavity including olfactory neuroblastoma , a tumour arising from olfactory epithelium cause anosmia. Various neurodegenerative conditions can diminish olfaction. A number of air-borne and water borne toxins can damage olfactory epithelium. Atrophy of the olfactory bulb may be present even at birth or secondary to an acquired disease leading to anosmia.

In the present study we have aimed to study the degree of affectation of the olfactory system in allergic rhinitis. Patients with allergic rhinitis typically present

with sneezing, watery nasal discharge, nasal obstruction, epiphora and heaviness of the head. Additionally, patients with allergic rhinitis often complain of decreased smell sensation. Objective assessment may reveal affectation to a variable degree, however. Very often, however, the sensation of smell is restored with appropriate therapy of nasal allergy. Some patients, however, do not recover completely.

In order to study the impact of allergic rhinitis on olfaction, we aim to present the results of subjective and objective assessment of the olfactory system in patients with allergic rhinitis both before and after initiation of therapy. Simultaneously, we will also assess the quality of life in patients with allergic rhinitis both before and after therapy.

Aims & Objectives

AIM

A cross sectional study to assess olfactory function and quality of life changes in patients with allergic rhinitis before and after medical therapy.

OBJECTIVES

1) To assess the prevalence of olfactory dysfunction in patients diagnosed with allergic rhinitis

2) To evaluate associated quality- of –life changes in patients diagnosed with allergic rhinitis

3) To assess the reversal of olfactory dysfunction and any change in quality –of-life in affected patients following medical therapy

Review of the literature

ANATOMY and PHYSIOLOGY

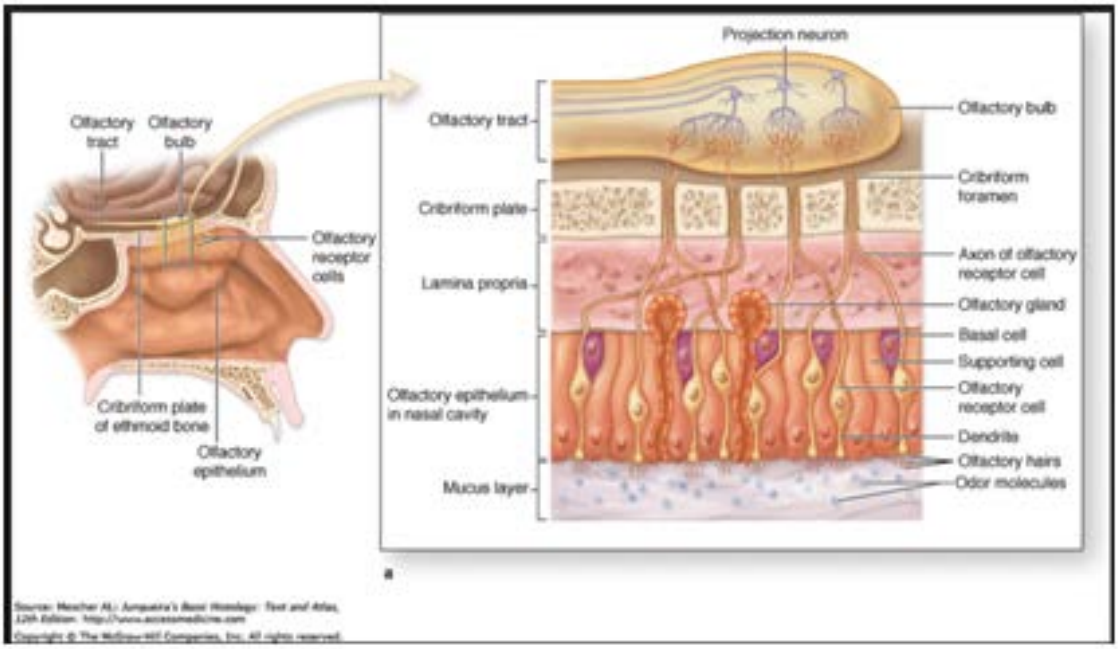
The nose is an important sense organ in the body and it performs two main functions. It acts both as a respiratory passage and organ of smell.

The nasal cavity extends from the nostrils to the posterior nasal apertures and is sub divided into right and left halves by the nasal septum. Each half has a roof, floor, and medial and lateral walls. Each half measures 5 cm in height, 5-7 cm in length, and 1.5cm in width near the floor. The width near the roof is only 1-2 mm. The nasal septum is a median osseocartilaginous partition between the two halves of the nasal cavity. The sensory nerve supply of the nasal septum is mainly derived from trigeminal nerve. The superior part of the septum is supplied by the internal nasal

branch of the anterior ethmoidal nerve. The posteroinferior part is supplied by the nasopalatine branch of the pterygopalatine ganglion. Special sensory nerves or olfactory nerves are confined to the upper part or olfactory area(3).

Olfactory area in humans

This is an area located approximately 7 cm from the anterior end of the nasal cavity in the roof. It is approximately 1 square centimetre in area and includes the cribriform plate and adjacent areas of the septum and lateral wall of the nose.This area can be distinguished from the rest of the nasal mucosa because of its yellow colour(4)



Chemosensory elements in humans

Human chemosensation comprises of 4 distinct elements.

1.Nervus terminalis..

This has been identified as terminal nerve system which is called as cranial nerve zero(5).

2.Main olfactory nerve i.e. olfactory nerve

3.Vomeronasal or accessory olfactory system

4.Trigeminal sensory system

Olfactory nerve which is the first cranial nerve mediates the sense of smell and the perception of flavour. This nerve innervates the olfactory epithelium which is present at the cribriform area(6).

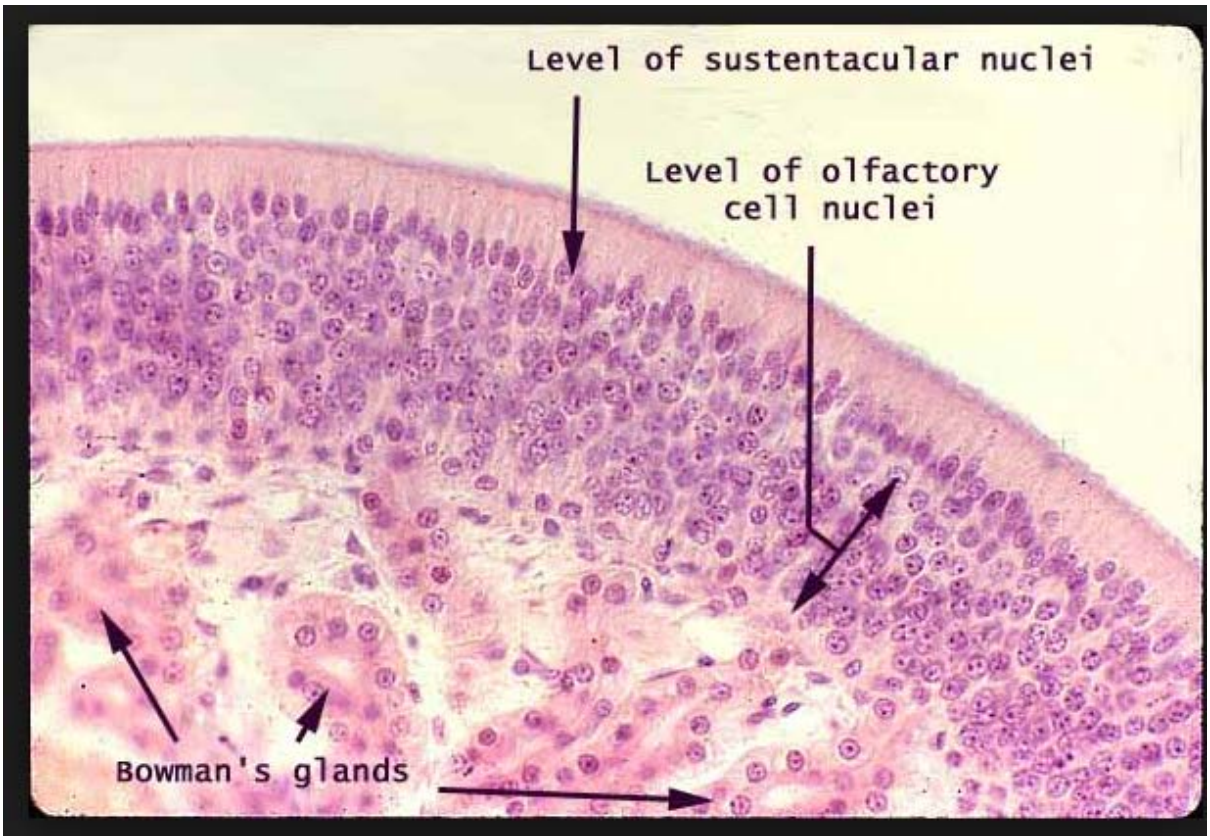
Free nerve endings of the trigeminal nerve which is the fifth cranial nerve innervates the entire nasal cavity. The nerve endings are sensitive to irritation, burning , cooling and tickling sensations. The odorants which are in high concentration stimulate these nerve endings and they initiate reflexes which increase secretions from nasal mucous glands, halts the inhalation of potentially noxious and harmful substances which can damage the lower airway. Cranial nerve zero which has been described in all the vertebrates including humans comprises of a loose plexus of nerve fibres in the nasal cavity. These nerves are identified with their nodal points which are present at the end of these nerve fibres(7).

Histology of olfactory epithelium

Olfactory epithelium which lines the nasal cavity serves the special purpose of olfaction. It is a pseudostratified columnar epithelium and it contains olfactory receptors beneath the cribriform plate in the nasal vault. Olfactory epithelium consists of 4 different types of cells which are olfactory cells, supporting cells, basal cells and brush cells. Olfactory mucosa is histologically made of three layers, epithelial layer,basal lamina and lamina propria which adheres to the underlying bone or cartilaginous tissue

Olfactory cells

These cells consist of the cell bodies of bipolar neurons which aggregate to form the olfactory nerve. The nerve fibres pierce the cribriform plate and terminate on the dendrites of mitral cells lying in the glomeruli of the olfactory bulb. The apical poles of the neurons are covered with non motile cilia and they have olfactory receptors. These receptors contain odorant binding proteins which are dissolved in the secretions of the Bowman's glands. The process of dissolving of these proteins in the secretions of Bowman's glands is essential for the process of olfaction.



Supporting cells

These cells are also called sustentacular cells. They are similar to neural glial cells

and act as metabolic and physical support for the olfactory cells(8). The nuclei of these cells is more apical than the epithelial cells

Basal Cells

These cells lie on the basal lamina of the lining epithelium. These are stem cells which are capable of division and differentiation into either a supporting cell or olfactory cell. This constant division causes olfactory epithelium to be replaced in every 2-4 weeks. These cells can be of two types: horizontal basal cells which lines the olfactory epithelium and more superficial globose basal cells(9).

Brush cells

These are columnar cells which bear microvilli and help in transduction for general sensation. The nerve fibres are terminal branches of trigeminal nerve. These act as afferents for non- olfactory signals

Bowmans glands

Bowman's glands are tubuloalveolar glands located in the lamina propria of the olfactory epithelium which secrete mucus. These glands are also called olfactory glands. They deliver a proteinaceous substance to the surface of the mucosa. These secretions trap and dissolve odorants and present them to the bipolar neurons. Old odors are washed away by the constant flow from these glands(10).

Embryology of Olfaction

Embryologically, olfactory receptors are derived from the neuroblasts which

differentiates to form olfactory placodes. Invagination of the central part of olfactory placodes forms the olfactory sac. The olfactory sac opens anteriorly and the olfactory organ is the only organ in the body where the cell bodies lie in direct contact with external environment.

Olfactory pathway

The olfactory pathway can be broadly divided into a peripheral system which receives the odorant stimuli and a central pathway that processes the stimulus so generated. The olfactory nerve, like the optic nerve, is considered as part of the central nervous system, however.

Upto 10- 20 million olfactory cells are present in the nasal mucosa and the cell bodies of these cells act as primary olfactory receptor neurons(ORN). The proximal end of the ORN which has unmyelinated axons joins to form myelinated fibres which are called fila olfactoria. There are about 15- 20 foramina in the cribriform plate.The olfactory fila pass through the cribriform plate to synapse in the olfactory bulb. As the pathway is short which communicates the nasal cavity with the central nervous system, there is a higher chances of damage in this pathway and higher risk of spread of infection from the nasal cavity to the central nervous system.

The olfactory cilia project down into the mucous layer which is rich in lipids. This mucous is secreted by Bowmans glands which resides in the olfactory epithelium and helps in transporting the odorant molecules which interact with the olfactory receptors which produce the signal of smell to the brain.

Above the mucus layer rests the base of the olfactory epithelium which has basal cells which divide through mitosis which later form the olfactory receptor neurons and the turnover of these neurons is 40 days. The receptor neurons has pigmented cells which are light yellow in humans and the depth of the colour correlates with olfactory sensitivity

Theories of Olfaction

The steric theory of Odour

Linus Pauling in 1946, illustrated that the specific odour quality is due to the molecular shape and size of the odor molecule.He suggested that the chemical molecules which are air borne are smelt only when they fit into the specific receptor sites. This was like a lock and key mechanism. This receptor is then activated and couples the G-protein and the signal transduction cascade begins.

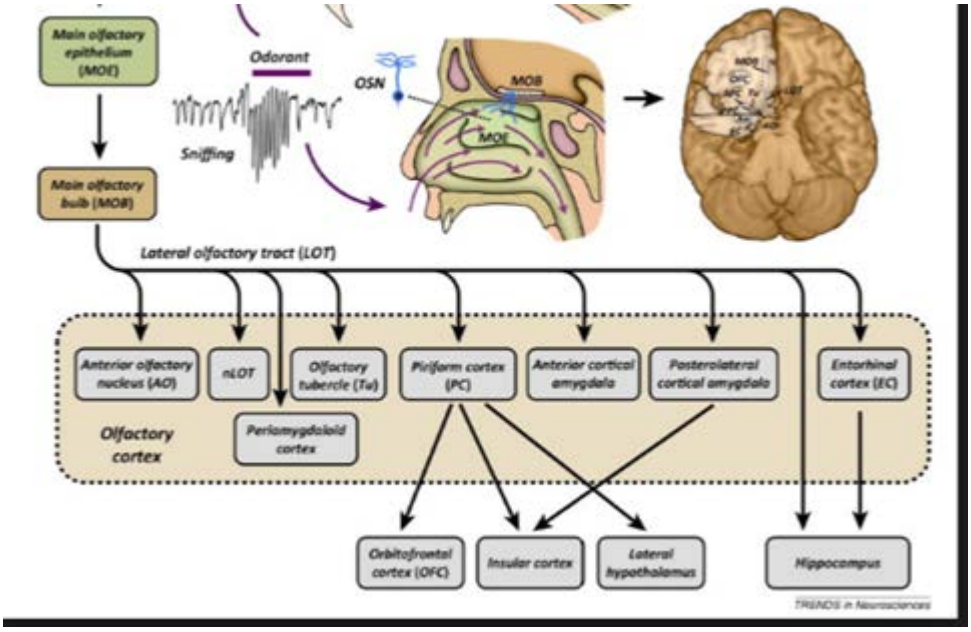
The vibrational theory of olfaction

Dyson suggested this theory which states that the vibration of a specific molecule is associated with odour. This validity of this theory did not last after 1970 as there were different enantiomers (molecules which are not mirror images of each other) which were described which have same spectrum in the infra red zone but smelt different.

Central Pathway for olfaction

Olfactory receptor neurons extend to contact odorants in the atmosphere on one side of the cribriform plate of ethmoid, while on the opposite side the neuronal

cells bundle to form groups which penetrate the cribriform plate, reaching the olfactory bulb where they converge. In the olfactory bulb a complex coding and decoding process occurs before the signals are sent to various parts of the central nervous system. The detection of odorants starts with a sniff causing turbulent airflow , odorant dissolving into the mucosa which are transported by chaperons which are the transport molecules to the specific odorant binding protein, thus producing the olfactory signal. The second method in olfaction is retrograde, whereby the odorants which arise from the nasopharynx ascend into the choana, thus reaching the olfactory epithelium.This is an important pathway for the perception of the flavour of the food. The olfactory epithelium is provided with myelinated fibres from the trigeminal nerve. The distal fibres of the trigeminal nerve are between the supporting cells under the epithelial surface and here they are unmyelinated. They respond to sensory stimuli. After leaving the olfactory bulb, the second order neurons form the olfactory tract. This tract passes along the base of the frontal lobe and enters in a complex pattern in the pyriform cortex, anterior commisure, caudate nucleus, olfactory tubercle, and anterior limbus of the internal capsule with secondary connections. Here it reaches the olfactory cortex where there is perception of smell.



Effect of olfaction with ageing and in disease

Olfaction can be disrupted in various diseases. There is perceptual interweaving of the odour and taste. There is also replacement of the olfactory epithelium with respiratory epithelium and loss of bulb neurons as age progresses .

Causes of smell impairment

Intranasal airway obstruction

- Trauma
- Edema
    - Allergic, including polyps and vasomotor rhinitis
    - Inflammatory ededma
- Exudates
- Neoplasms

Intranasal mucosal destruction

- Atrophic rhinitis
- Ageing (mucosal replacement)
- Viral infections
- Toxic chemicals and drugs

Head trauma

- Fracture of the cribriform plate
- Shearing laceration of the olfactory nerves
- Haemorrhage causing intereference with frontal lobes, olfactory bulbs or tracts

Intracranial lesions

Endocrine

- Kallmans syndrome
- Turners syndrome

Psychiatric problems

Tests of olfaction

There are various tests to assess olfactory dysfunction in patients. The tests include the Sniffin' sticks test(11), UPSIT(University of Pennsylvania Smell Identification test)(12) and CCCRC test(Connecticut Chemosensory Clinical Research Centre)(13). The CCCRC test which is widely used consists of 3 components, viz., threshold testing using butanol, odour identification and odour discrimination. In the butanol threshold test, n -butyl alcohol, a sweet smelling substance, is tested at different concentrations.

Each nostril is tested separately. The point of transition between no detection of smell to identification of smell is considered as the threshold for that individual. Based on the results of the 3 components of the CCCRC test, a composite score is calculated. A diagnosis of anosmia, hyposmia and normosmia may be made, depending on the composite score obtained. As the CCCRC test is easy to perform and can be administered within a few minutes, it is the preferred test for assessment of olfaction.

Allergic rhinitis

Allergic rhinitis is a disorder of the nose induced after the exposure to allergen. This is due to IgE mediated inflammation of the membranes lining of the nose(15). The three cardinal symptoms affecting the nose in allergy are sneezing, nasal obstruction and mucous discharge. Allergic rhinitis is a global health problem and a major illness causing disability with a prevalence of . Patients from different countries, different ethnic groups and different ages suffer from this. Allergic rhinitis affects social life, work and scholastic performance. The economic burden of the disease is always underestimated(16).

Allergic rhinitis is an inflammation of the lining of the nose and is characterized by anterior or posterior watery rhinorrhoea, sneezing, nasal blockage and itching

of the nose wherein the symptoms occur on 2 or more consecutive days for more than one hour on most days. There may be associated ocular symptoms(17).

It is the most common form of non- infectious rhinitis.There is a marked increase in the IgE response against allergens in allergic rhinitis.(18). Since the nasal mucosa is

continuous with that of the paranasal sinus mucosa, congestion of the ostia can result in inflammation and obstruction to the paranasal sinuses.

Pathophysiology of sinonasal allergy

The pathophysiology of allergy is a complex process which involves cell mediators, chemokines, neuropeptides and adhesion molecules.It is a type 1 hypersensitivity reaction. The reaction is considered in 4 phases.

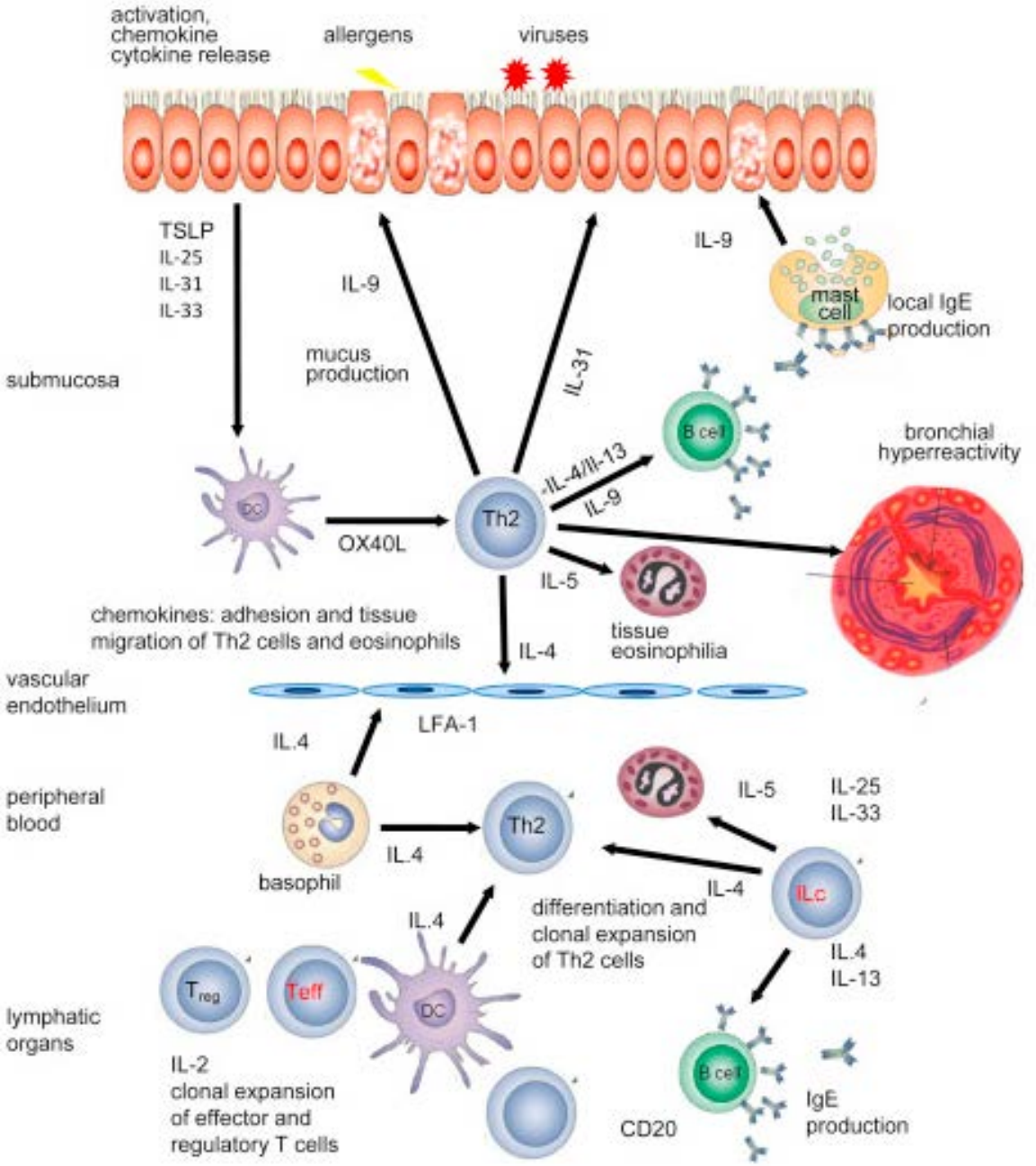
1. Sensitization
2. Early phase reaction: subsequent reaction to allergen
3. Late phase reaction
4. Systemic activation

1.Sensitization

Allergens are harmless molecules which do not elicit symptoms in non atopic individuals. Every allergen has an antigenic epitope which is that part of the allergen that is the antigenic determinant which is recognised by antibodies, T cells or B cells.

It is that specific region of the allergen where the antibody or immune cell binds. In individuals who are sensitive, these allergens are not completely cleared by the mucociliary system and are presented to Langerhans cells and dendritic cells which are antigen presenting cells which lie in the epithelium and lamina propria of the nasal

mucosa. These cells contain Birbeck granules which increase in number on exposure to allergen. The activation of these antigen presenting cells is very important for the activation of T lymphocytes which are located in the local lymph nodes. The epithelial surface of the human nasal mucosa has the highest network of thedendritic cells numbering > 500 per mm3.The epitopes of the allergen are presented by the antigen presenting cells to the T cell lymphocytes in the local lymph nodes. The majorhistocompatibility complex (MHC) is a set of cell surface proteins which the epitopes of the allergens, bind to them and display them on the cell surface for recognition by T cells. In humans, the MHC is also called human leucocyte antigen (HLA).Th 2 cells are lymphocytes which are a subset of T cells present in local lymph nodes which are produced by activated T cell lymphocytes. The stimulation of Th2 cells produces cytokines. The activated Th2 cells then stimulate B cells which also recognise the allergen through its epitope and MHC. The activated recognize B lymphocytes in the local tissues are stimulated toproliferate, form plasma cells and migrate into the lining of the nasal mucosa and produce IgE antibody.



Once Ig E is produced, it is specifically taken up by the mast cells. The IgE which then circulates in the blood stream then recognises the epitope of the allergen every time it is exposed to it. The patient is thus sensitized and responds to subsequent contact with an allergic response.

2. Early Phase Response

The release of histamines, cytokines and prostaglandins in nasal mucosa cause allergic symptoms like sneezing, rhinorrhoea and itching. These symptoms occur within minutes of release of these mediators and are associated with them. When an allergen is cross linked with an IgE, and this complex is attached to the mast cells, there is degranulation of the mast cells and all the mediators for allergen response are released. These mediators can be released from mast cells or from the arachidonic acid on the cell membrane of the mast cells. Histamine is the most important mediator which causes symptoms of allergic rhinitis. Its action on the sensory nerve endings causes itching and sneezing. Its action on endothelial cells causes vasodilatation, plasma exudation and oedema. Histamine acts directly on the mucous cells on the ipsilateral side and on the contralateral side of the nasal cavity it acts through neural reflex.

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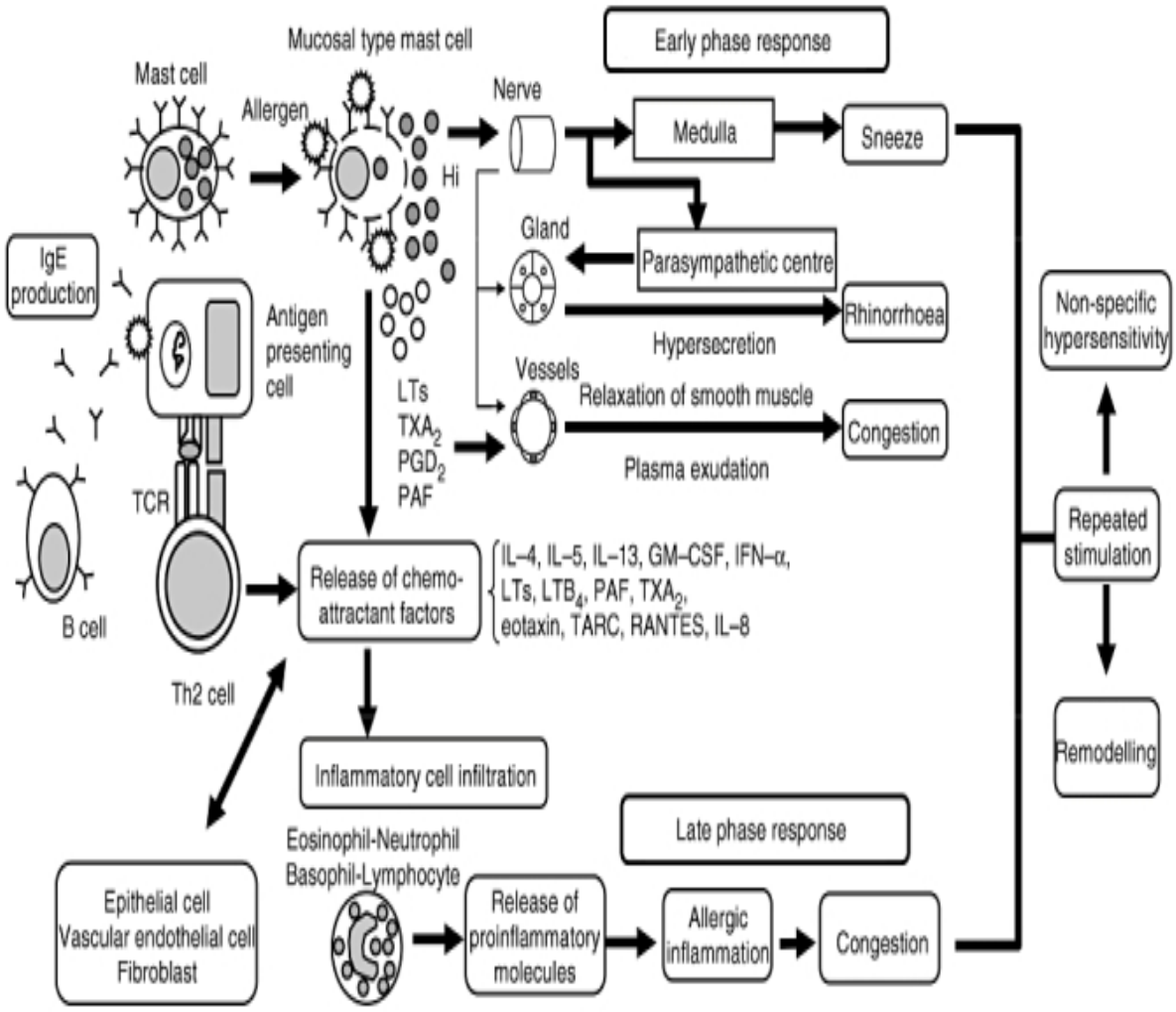


reflexes. Histamine acts as the most important mediator in the early phase and to a limited extent in late phase by acting on the basophil cells. It also has pro inflammatory and immune modulatory properties. It increases the production of IL-6 and IL-8 by activation of vascular endothelial cells with consequent cytokine production. PG D2 (prostaglandin) is the predominant prostanoids which is released.

This plays a major role in sustained nasal obstruction. Leukotrienes play an essential

role in asthma and rhinitis. This includes sulphidopeptide leukotriene which belongs to the family of eicasonoids generated by lipoxygenase pathway. These increases the vascular permeability and causes edema in the nose and recruits eosinophils and neutrophils. Kinins may also be involved in allergic rhinitis, in early and late phases. These are generated from plasma proteins by the action of kininogen. Kinins are found in nasal secretions following allergic response and are found to cause rhinorrhoea, sneezing, obstruction and pain. Preformed mediators are released by degranulation of the mast cells which include Th2 cytokines such as IL-4, IL-5, IL-13, and proinflammatory cytokines such as IL-6, IL-8, IL-I0 and TNF-alpha. The release of Th2 cells is very important in the regulation of IgE response. The number of mast cells usually increase in the nasal mucosa during episodes of seasonal allergy.

3. Late phase response

If high doses of allergen is used there is a late phase response in around 50 %of the individuals. This is primarily an inflammatory response and includes variety of cells like macrophages, eosinophils, basophils, mast cells, T cells and neutrophils into the local reaction site. Late phase response causes nasal obstruction and hyperactivity.

INFLAMMATORY CELLS AND THEIR REGULATION IN ALLERGIC RHINITS

MAST CELLS

In allergic rhinitis patients, mast cells are found to be in abundance in the nasal mucosal epithelial compartment. Mast cells play the central role in mechanism of allergic rhinitis. Iranietal(19) described two types of mast cells depending upon the type of proteases they express. MC (T) that produces tryptase and MC (TH) that produces chymase. In

allergic rhinitis, MC (T) type of mast cells are seen. Mast cells release mast cell mediators and a variety of cytokines like IL- 4, IL-10. IL-6, IL-13. Mast cells causes extra cellular matrix interaction which up regulate the cytokine production. This mechanism helps in mast cell activation even when the concentration of antigen is very low in the environment. Mast cell induces Ig-E synthesis in B cells and activate IgE-IgE receptor cascade. Therefore mast cells act as the mediator for immediate response and also as an immune regulator for the ongoing inflammation process both in intermediate and late phase reactions.

BASOPHILS

Basophils are found in the nasal secretion of patients in allergic rhinitis. They also play an important role in allergic inflammation. They are usually not present in peripheral cells and hence not seen in any of the nasal epithelial cells. The number of basophils relate with the severity of the disease. They release histamine and cytokines like IL-4 and IL-3 and they are primarily concerned with late phase recation

EOSINOPHILS

In any chronic allergic disease, eosinophils have an important role to play. They are derived from a progenitor cell CD34+. These cells will either develop as eosinophils or basophils. Eosinophils havebilobed nucleus and they are orange coloured cells. They are also not present in any of the nasal mucosal cells.

Their concentration is highest in nasal secretions. Eosinophilic Cell Protein is the major constituent of nasal secretions. In the tissue , cytokines like IL-5 keep eosinophils alive for several days by overcoming programmed cell death. Then eosinophils are matured. These mature eosinophils contain MBP, ECP and eosinophil derived neurotoxin and eosinophil peroxidise. They synthesize and release cytokines such as IL-3, IL-5, proinflammatory cytokines that play an important role in the late phase.Wang etal studied ECP in nasal secretions of 18 atopic patients and 10 healthy volunteers. Allergen challenge in these atopics induced an increase in eosinophils that persisted for 10 h and was less at 24 h, whereas levels of ECP in these atopics peaked at 24 h indicating possible degranulation.

T LYMPHOCYTES

They are among the principal factors that regulate the allergic immune response in allergic rhinitis. Th1 cells predominantly release IFN- gamma and IL-2 and they are primarily responsible for the delayed hypersensitivity. Th 2 cells are responsible for IgE release and allergic response. Inflammation of the mucosa is characterized by infiltration of T lymphocytes both in mucosa and sub mucosa. This causes a cascade increase in all the cytokines which regulate the allergic response and induces IgEsynthesis by B cells

MACROPHAGES

Allergic reactions occur in a mucosal environment that is rich in both dendritic cells and macrophages. However, there are significant differences between the

lower and upper airways, as alveolar macrophages form more than 90% of the cell population in bronchial alveolar lavage , but airway macrophages on the nasal epithelial surface just account for about 1 to 2% of the cells. Still, in seasonal and perennial allergic rhinitis, a significant increase in macrophages has also been found in the nose .Langerhans cells represent an important group of dendritic cells in the nose, characterised by the expression of CD1 and Birbeckgranules . These cells increase after allergen challenge or in patients with allergic rhinitis and may serve as antigen presenting cells in the upper airway.

EPITHELIAL CELLS

Epithelial cells are present in the mucosa of the nasal epithelium. Their primary action is about secretion of mucus and removal of foreign body by the action of their cilia. They also have a wide range of immunomodulatory activity by the release of eicasnoids, endopeptidases, chemokines and cytokines. Itis now appreciated that allergens, on account of their enzymatic proteolytic activity can directly activate cells . House dust mite allergens have been shown to activate epithelial cells *in vitro*,inducing cytokine and chemokine release and thus can induce airway inflammation independent of IgE. It has also been shown that epithelial cells in allergic individuals are more sensitive to air pollutants like diesel exhaust particles and this has been attributed to the greater constitutive and pollutant induced release of pro-inflammatory cytokines

ONGOING INFLAMMATORY PROCESS

Structural cells like epithelial cells, residential cells like mast cells and the infiltrated inflammatory cells like eosinophils, basophils and T cells all play a role in inducing and maintaining on-going allergic inflammation. While cytokines like IL-4, and IL-13 released from mast cells and T cells help drive B cells toward IgE synthesis and could contribute to the local IgE synthesis in the nasal mucosa of patients with allergic rhinitis

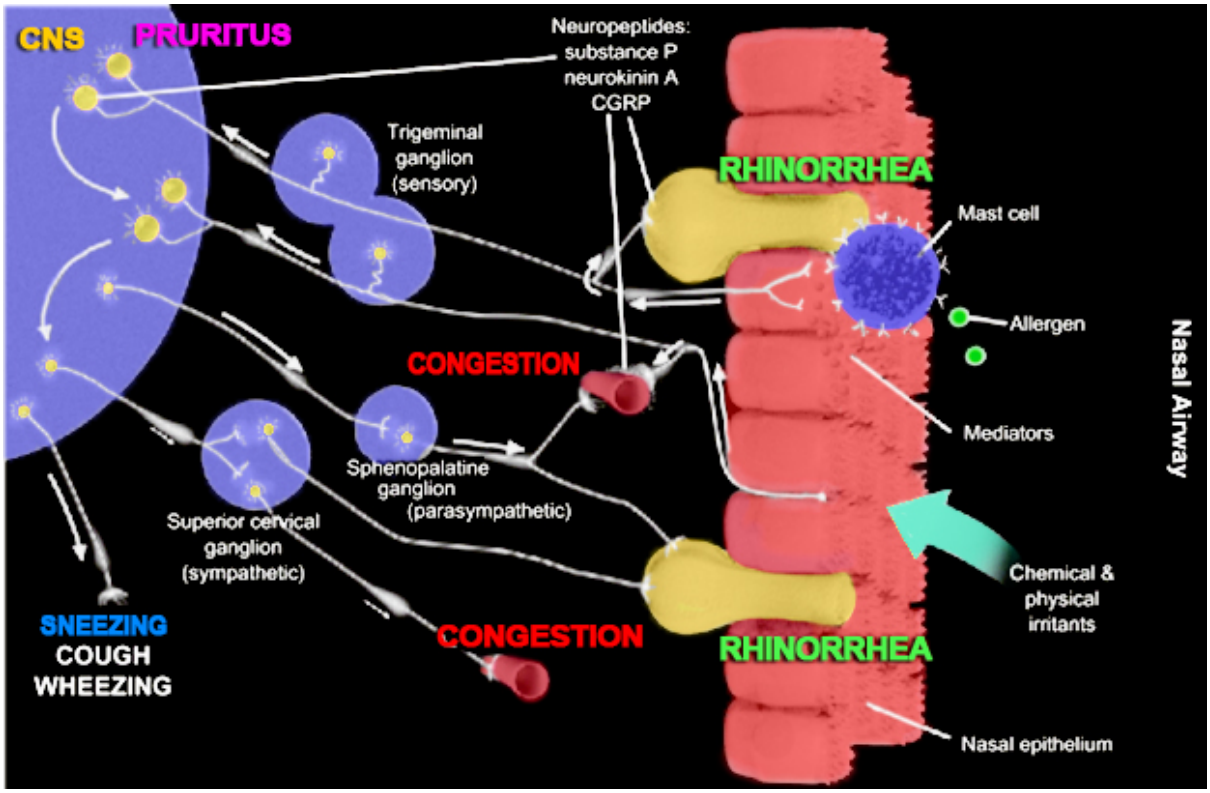
SYSTEMIC ACTIVATION

Allergic Rhinitis is not just associated with local response but also a systemic response. This response helps us to explain the link between the patients who have rhinitis and asthma. In patients with AR without asthma produces inflammatory response in both the upper and lower airway and increased bronchial activity. In sensitized individuals, allergen exposure causes a release of many inflammatory cells and few cells migrate to bone marrow and this recruits the inflammatory cells like eosinophils and basophils to the target organs.

Clinical manifestations of sinonasal allergy

It is a recently recognised that allergic rhinitis symptoms include more than the classical watery rhinorrhoea, sneezing and nasal block. It is associated with the impairment of day to day life of individuals.There is a significant impairment in the quality of life of both the adults and children(20). There can be an impairment of general activities,

social and emotional impairment of the normal function of the individuals(21). Poor control of the symptoms has a significant impact on the sleep pattern.



There is a genenral impairment in the overall function of the individual at work or at school(22). The severity of the allergic rhinitis is based on the severity of the impairment of the normal function of an individual when compared to the other normal individuals(23).

Effect of olfaction in allergic rhinitis

Allergic rhinitis(AR) is a common inflammatory disease prevalent world wide affecting 10-25% of the population(24). Some studies have shown that the prevalence of olfactory dysfunction in allergic rhinitis ranges from 21%-23 %(25).Further, olfactory dysfunction is worse in patients with seasonal AR during the season, than in patients

with perennial AR. There are 2 potential causes for olfactory dysfunction in AR, viz., inflammation and obstruction.The degree of blockage is not related to the degree of olfactory dysfunction. This suggests that olfactory dysfunction is secondary to inflammatory response which occurs in the nasal cavity(26).

Becker etal have studied olfactory dysfunction using the sniffin' sticks test in seasonal and perennial AR and correlated the results with analysis of nasal secretions and inspiratory rhinomanometry. Of a total of 72 patients, 23 were proven seasonal AR , 16 were perennial AR and 33 healthy volunteers. The authors concluded that nasal flow rhinomanometry did not show any significant difference in the three groups. However, olfactory thresholds were significantly less in the AR group when compared to the normal control group. Further, there was not much difference in the score between the seasonal and perennial AR groups. On analyzing the nasal secretions, it was found that increased levels of eosinophilic cationic protein was present in patients with AR compared to the control group(27). Guilemany et al studied the impact of sense of smell in patients with persistent AR. They studied 49 patients with persistent AR and 60 controls. The authors found that there was significant olfactory dysfunction in patients with persistent AR when compared to the control group.All these patients were positive for skin allergy test(28).

Some studies have shown that olfactory dysfunction improves in patients who are treated with intranasal steroids. The mechanism behind this is unclear. It is possible that reduction of the oedema or inflammation is the cause for this phenomenon. Other studies have shown a significant reduction in the number of eosinophils in the olfactory cleft following therapy with topical steroid. In this study

using the topical steroid mometasonefuroate in a group of patients with AR, the improvement in inflammation was significantly higher in patients who were administered mometasonefuroate compared to placebo, showing that inflammation is significantly reduced in patients using mometasonefuroate(29). Stevens et al studied the response to topical nasal and oral steroids in patients following endoscopic polypectomy(30). In this prospective study, 24 patients who were anosmic prior to endoscopic and nasal surgery, were selected. Most of the patients had either bronchial asthma or AR or both. Twelve out of 24 remained anosmic postoperatively and did not respond to either nasal steroids or oral steroids. More patients responded to oral than topical steroids, however. Alobid et alstudiedthe effect of oral and intra nasal steroids in severe nasal polyposis. They randomised the patients into two groups after 4 weeks of steroid washout period. The first group was given 2 weeks of oral steroid followed by 12 weeks of intranasal steroids. The control group which included 22 subjects did not receive any steroid treatment .Barcelona Smell Test 24 (BAST-24), nasal congestion, tissue eosinophilia, and nasal nitric oxide were assessed.The authors found that combined nasal and oral steroids improved olfaction in the cases but not the controls(31). Very few studies have evaluated the change in olfaction following medical therapy of AR without polyposis.

Diagnosis of allergy

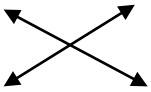
The diagnosis of Allergic rhinis is based upon the concordance of the history and diagnostic tests. The typical symptoms include watery nasal discharge, sneezing and nasal obstruction. Occular symptoms are seen in patients with outdoor allergens.

Diagnostic tests include skin allergy test and an increased IgE levels in the blood. Skin Allergy test which is commonly used is prick and puncture test(32). The modified skin prick test by Pepys is the current test which is commonly used(33). Negative and positive controls are used in this test. Negative control consists of the diluents which are used to preserve the allergen vaccine(34). A rare dermographic patient can produce wheal and flare to the diluents which are used(35). Positive control is used to detremine the supression by medication and the technique of administartion of the test. The usual positive control which is used is histamine dichloride (36)

Classification of allergic rhinitis

Intermittent symptoms
- ≤4 days per week
- Or ≤ 4 weeks

Persistent symptoms
- 4 days per week and > 4 weeks



Mild
- Normal Sleep
- Normal daily activities
- Normal Work and School
- No troublesome symptoms

Moderate-Severe
One or More Items
- Abnormal sleep
- Impairment of daily activities sports, leisure
- Problems cause at school or work
- Troublesome symptoms

Quality of life in sinonasal allergy

Allergic rhinitis causes impairment in the performance of daily functions by patients thus affecting the quality of life both in children and adults. Patients can also suffer from sleep disorders, emotional problems and imapirment in routine social activity and social functioning.

Olfactory function is an important component of quality of life (QOL) and mental health in patients with sinonasal disease(37). Various indicators have been used to assess the quality of life in patients with sinonasal disease. These include SF-36 QOL(short form health survey), SNOT 22(sino nasal outcome test), ESPRINT 15. RSDI(rhinosinusitis disability index), RQLQ (rhinoconjuctivitis and quality of life) and HRQL (health related quality of life). SF -36 is a generic QOL instrument which does not specifically address olfaction or allergy(38). In contrast, the ESPRINT-15 (short-form instrument to measure health-related quality of life in adults suffering from allergic rhinitis) questionnaire, which was first developed and validated on a Spanish population, is unique in that it assesses QOL in patients with allergic rhinitis(39). The instrument contains 15 items covering 5 domains, viz. Symptoms (5 items), daily activities(3 items), sleep (3 items), psychological affectation(3 items) and wellness (1 item). Items are scored using a 6 point Likert scale, ranging from 0 to 6. In a study on patients with mild, moderate and severe AR, Valeroetalfound that there were significant differences in the global score and individual scores of ESPRINT QOL between the various categories. Juniperetalhave designed RQLQ questionnaire to assess the quality of life in patients with rhinoconjunctivitis with or without allergic in origin. This questionnaire is used in adults between 17-70 years of age. The RQLQ has 28 questions

in 7 domains (activity limitation, sleep problems, nose symptoms, eye symptoms, non-nose/eye symptoms, practical problems and emotional function). There are 3 ‘patient-specific’ questions in the activity domain which allow patients to select 3 activities in which they are most limited by their rhinoconjunctivitis. Patients recall how bothered they have been by their rhinoconjunctivitis during the previous week and to respond to each question on a 7-point scale (0 = not impaired at all - 6 = severely impaired). The overall RQLQ score is the mean of all 28 responses and the individual domain scores are the means of the items in those domains.

A number of studies have shown improvement in QOL after therapy in patients with AR. Mir etal in their review have concluded that the burden of AR on school going children and the impact of it on their quality of life is significant . They have also found that intranasal corticosteroids have been the best treatment in AR thus far .Canonica et alhave studied the effect of quality of life in AR. They used an online survey and telephonic interview of 3635 people with AR. The authors found that many patients have poor quality of life secondary to AR .Kalpiagolu et alsimilarly evaluated the quality of life in patients with asthma and AR and a combination of both.They studied a total of 316 patients out of which 232 had AR, 40 had asthma and 44 had both diseases. The authors used the SF 36 and HRQL questionnaire to assess the quality of life. They found that AR has a minor role on quality of life. Juniper et al validated and developed a questionnaire to assess the quality of life in children with rhinoconjunctivitis.The authors developed a questionnaire which was accurate and sensitive to the changes of quality of life in children. This questionnaire is frequently

used to assess QOL in patients with AR.

Therapeutic Options in Sinonasal allergy

Histamine

Pharmacology

The biogenic amine, histamine acts as a major mediator for inflammation and anaphylaxis and gastric acid secretion and a major role in neurotransmission. It acts through 4 classes of receptors

Chemical structure

It's a hydrophilic molecule consists of an imidazole ring and an amino group. These two rings are connected by two methylene groups. The pharmacologically active form of the histamine is the monocationic form. H3 and H4 receptors have a higher affinity that H1 and H2. The four receptors can be activated by any nalogue of histamine.

Distribution and Biosynthesis of Histamine

Histamine is present in almost all the mammalian tissue ranging from <1 to >100microgm. The mast cell is the predominant storage site for the histamine in most tissues. The concentration is high in those cells where mast cells are high like skin, bronchial mucosa and intestinal mucosa.

Synthesis, storage and Metabolism

Its formed by the decarboxylation of the amino acid histidine by the enzyme L-Histidine decarboxylase. This enzyme is present in the every mammalian tissue that contains histamine. The chief site of storage is the mast cell in tissues, basophils in the

blood. These cells store histamine in secretory granules and they have the ability to synthesize histamine. Non mast cells sites of histamine formation consists of gastric mucosa, epidermis and neurons within the CNS. Turnover is rapid at the non mast cell site as the histamine is not stored but released continuosly. There are two major paths of histamine metabolism in humans. The most important one is ring methylation to form N-methylhistamine . Most of the N-methyl histamine is then converted to N-methyl imidazole acid by monamineoxidase(MOA)

Release and functions of endogenous histamine

Histamine plays a central role in immediate hypersensitivity and allergic responses. As it is released from the storage granules, it interacts with IgE antibody on the mast cell surface. And thus participates in the entire hypersensitivity response. Histamine has a major role in neurotransmitter release and also gastric acid secretion.

Role in Allergic Response

The principal target cells of immediate hypersensitivity is mast cells and basophils. As a part of the allergic response to an antigen. IgE antibodies are generated and bind to the surface of mast cells and basophils via a receptor. Antigen bridges the IgE molecule via FceR1 and activates signalling pathways in mast cells and basophils.

Pharmacological Effects

Receptor-effector coupling and mechanisms of action

Histamine receptors are GPCR . H1 receptor is coupled to GQ11 and activate adenylyl cyclase pathway, where as H3 and H4 receptors inhibit adenylyl cyclase pathway.Stimulation of H1 receptors on smooth muscle cause contraction, whereas stimulation of H2 receptors on smooth muscle cause relaxation..

Histamine Receptors

Ash and Sehild predicted the existence of histamine receptors.

H1 and H2 receptors

These receptors are widely distributed in the peripheral and central nervous system..Histamine exerts local or wide spread effects on smooth muscles and glands.It causes itching and stimulation of secretion from nasal mucosa. In lungs it contracts the bronchial smooth muscles and in gut causes contraction of smooth muscles and apotent stimulator of gastric acid secretion. Bronchoconstriction and contraction of gut and nasal mucosal secretion are mediated by H1 receptors. Gastric acid secretion are mediated by H2 receptors.

H3andH4 receptors

H3 receptors are auto receptors. They inhibit histamine release and modulate releasof otherneurotransmitters.H3 receptors high constitutive activity, histamine release is tonically inhibited and inverse agonist will thus reduce receptor activation and increase histamine release from histaminergic neurons. Therefore H3 agonist promote sleep and antagonist promote wakefulness.H4 receptors are found in cells of haematogenic origin like eosinophils, basophils, monocytes and mast cells. Activation of H4 receptors in these cells induces cellular shape change, chemotaxis , secretion ofcytokines and up regulation of adhesion molecules. This suggest that, H4 antagonist can be used in inhibiting allergic and inflammatory response.

Effect of histamine release on increased capillary permeability

The effect of histamine on small vessels causes efflux of plasma protein and fluid into extracellular spaces and increases lymph flow thus causing edema.H1 receptors are the major mediators of this response. Increased permeability is caused by histamine activation of H1 receptors on post capillary venules. This contracts the endothelial cells and exposes the basement membrane which is freely permeable to plasma proteins and fluid.

Triple response of Lewis

Intradermal injection of histamine produces a characteristic response known as the triple response. This consisits of

- Localised red spot a few millimetres around the site of injection within a few seconds and reaches its maximum in less than a minute.
- A brighter red ‘flush’ or ‘flare’ extending more than 1cm beyond the red spot develops more slowly.
- A wheal that is seen within 1-2 minutes occupies the same area as the original red spot.

Initial red spot results from direct vasodilating effect of histamine, flare is due to histamine induced stimulation of axon reflexes that causes vasodilation indirectly and wheal is histamines capacity to increase the capillary permeability

ANTIHISTAMINES

Antihistamine was first described by Bovet and Staub in 1937. The initial substance which was used in guinea pigs was too toxic for clinical use. By 1944, Bovet and his

colleagues described pyrelamine maleate an effective antihistamine which was used clinically. In 1980, non sedating antihistamines were developed for the treatment in allergic responses.

Pharmacological properties

Chemistry

All the H1 receptor antagonists are inverse agonists that reduce the constitutive activity of the receptors and compete with histamine. This causes antihistamine binding to the receptor thus causing inactive conformation. If a histamine binds to the receptor it causes active conformation. Like histamine, many of the antihistamines contain a substituted ethylamine moiety. Unlike histamines it's a tertiary amino group linked by 2 or 3 atom chains to two aromatic substances.

Mechanism of action

Immediate hypersensitivity reactions : Anaphylaxis and allergy

Histamine is the most potent autocoid released in hypersensitivity reactions. The symptoms ensuing its contributions varies from species to species. Therefore the protection offered by H1 antagonist also varies from species to species. In humans, itching and edema formation are well suppressed, however its effect on blood pressure is not very marked.

Capillary permeability

H1 antagonists block increased capillary permeability ,edema and wheal caused by histamine. H1 antagonists suppress the action of histamine on nerve endings, thus decreasing the flare component of the triple response.

Classification of antihistamines

Antihistamines which are used in allergic rhinitis belong to H1 antagonist group

These drugs are classified into classified into first and second generation antihistamines primarily based on the ability to cross the blood –brain barrier. The second generation antihistamines primarily act on the peripheral H1 receptors and have a reduced ability to cross the blood brain barrier. They are thus less sedating in action. The drugs included in these 2 classes are seen in the table .The differences between the 2 classes of antihistamines is also listed .

First generation antihistamines

- Tricyclic dibenzoxipens
- Ethanaloamines
- Ethylenediamines
- Alkylamines
- Piperazines
- Phenothiazines
- Piperadines

Second generation antihistamines

- Tricyclic
- Alkylamines
- Piperazines
- Piperadines
- Phthalaz

Chemical Classification of H1 antihistamine

Alkylamines	Ethanolamines	Ethylenediamines	Phenothiazines	Piperazines	Piperidines
Brompheniramine	Carbinoxamine	Antazoline	Promethazine	Buclizine	Azatadine
Chlorpheniramine	Clemastine	Tripelennamine	Trimeprazine	Cyclizine	Cyproheptadine
Dexchlorpheniramine	Dimenhydrinate	Pyrilamine	Mequitazine	Meclizine	Ketotifen
Pheniramine	Diphenhydramine			Oxtamide	Loratadine
Dimethindene	Doxylamine			Hydroxyzine	Desloratadine
Triprolidine	Phenyltoxamine			Cetirizine	Bilastine
				Levocetirizine	Ebastine
					Terfenadine
					Fexofenadine
					Levocabastine
					Mizolastine
					Rupatadine

First-Generation H1 antihistamines	Second-Generation H1 antihistamines
Usually administered in three to four daily doses	Usually administered once or twice a day
Cross the blood-brain barrier (lipophilicity , low molecular weight, lack of recognition by the P-glycoprotein efflux pump)	Do not cross the blood-brain barrier (lipophilicity , high molecular weight, recognition by the P-glycoprotein efflux pump)
Potentially cause side-effects (sedation/insomnia/hyperactivity/convulsions)	Do not cause relevant side-effects (sedation/fatigue/hyperactivity/convulsions)
Case reports of toxicity are regularly published	No reports of serious toxicity
No randomized, double-blind, placebo-controlled trails in children	Some randomized, double-blind, placebo-controlled trails in children
Lethal dose identified for infants/young children	Do not cause fatality in overdose

Therapeutic uses of antihistamines

H1 antagonists play an important role in the symptomatic treatment of various immediate hypersensitivity reactions.

Allergic diseases

H1 antagonists are most useful in acute allergic reactions with symptoms of rhinitis, urticaria and conjunctivitis. These drugs are treated for seasonal allergic rhinitis and conjunctivitis. They relieve the symptoms of sneezing, rhinorrhoea and itching of nose and throat. These drugs are used for acute phase of symptoms. They are not effective of chronic phase of symptoms.

Adverse effects

The most important adverse effect is sedation. The next important side effect is loss of appetite, nausea, vomiting, epigastric pain, constipation and diarrhoea. Owing to the antimuscarinic actions there are effects like dryness of throat, mouth and respiratory passages.

Antihistamines used in Allergic rhinitis

Cetrizine

It is a second generation piperazine. It has minimal anticholinergic effects. It has also negligible penetration into the brain but is associated with a higher incidence of drowsiness. The active enantiomer levocetrizine is more potent and less drowsy when compared to that of the first genetation drugs.

Fexofenidine

This drug is a second generation piperadine. They are highly selective H1 receptors. They lack significant anti cholinergic actions and penetrate poorly into the CNS.

Studies showing the efficacy of antihistamines in allergic rhinitis

La Force etal conducted a randomized, double blinded, placebo controlled multicentric

study, for 2 weeks, in patients with seasonal allergic rhinitis. The first week of the study was an open label period where all the patients received fexofenadine 60 mg twice daily. A small number (25-33%) of patients had persistent symptoms. These patients(334) were divided into 3 categories. The first group received only azelastine nasal spray, the second group received azelastine with fexofenidineandthe third group received placebo nasal spray each for 1 week of duration. The authors concluded that those patients who were administered azelastine nasal spray as monotherapy as well as those given fexofenidine and azelastine nasal spray together responded well for seasonal allergic rhinitis and showed no difference in their response.(41)Those patients that received placebo nasal spray showed

Berkowitz etalanalysed the results of two studies . These studies were double blinded randomized controlled studies which compared the effect of fexofenifine and pseudoephedrine with a placebo in seasonal allergic rhinitis. These studies recorded allergic rhinitis symptoms for 2 hours after dosing and 30 minute interval for 4 hours. The primary end point was the onset of action which was measured in the symptom

score. The secondary end point was to include the absolute and total change in the percent score of the symptoms. A total of 1693 patients were screened in which 786 were randomized. The authors concluded that the patients with fexofenidine had onset of action at 45 minutes and the effect lasted for a total duration of 6 hours. (42)Guilemanyetal studied the impact on smell in allergic rhinitis and reversal of the same after the use of antihistamines. The study group included 27 patients who had subjective loss of smell. This study was randomized double blind placebo study. Nasal

symptoms, endoscopy, skin prick test, acoustic rhinometry, peak nasal inspiratory flow, nasal nitric oxide and olfactory test (Barcelona smell test) were performed in all patients with persistent allergic rhinitis at baseline and after 7 days and 30 days of treatment with levocetrizine 5mg or placebo. The study population was randomized into 2 groups, with 14 receiving levocetrizine and 13 receiving placebo.

The symptoms score after 7 and 30 days were noted. Significant improvement in loss of smell was observed after 7 days of levocetrizine treatment. This study concludedthatlevocetrizine was effective against symptoms of persistent allergic rhinitis and also caused an improvement in the loss of smell. The improvement in olfaction was believed to be secondary to reduction in nasal inflammation rather than nasal patency(43).

INTRANASAL STEROIDS

Effect of steroids on inflammatory response

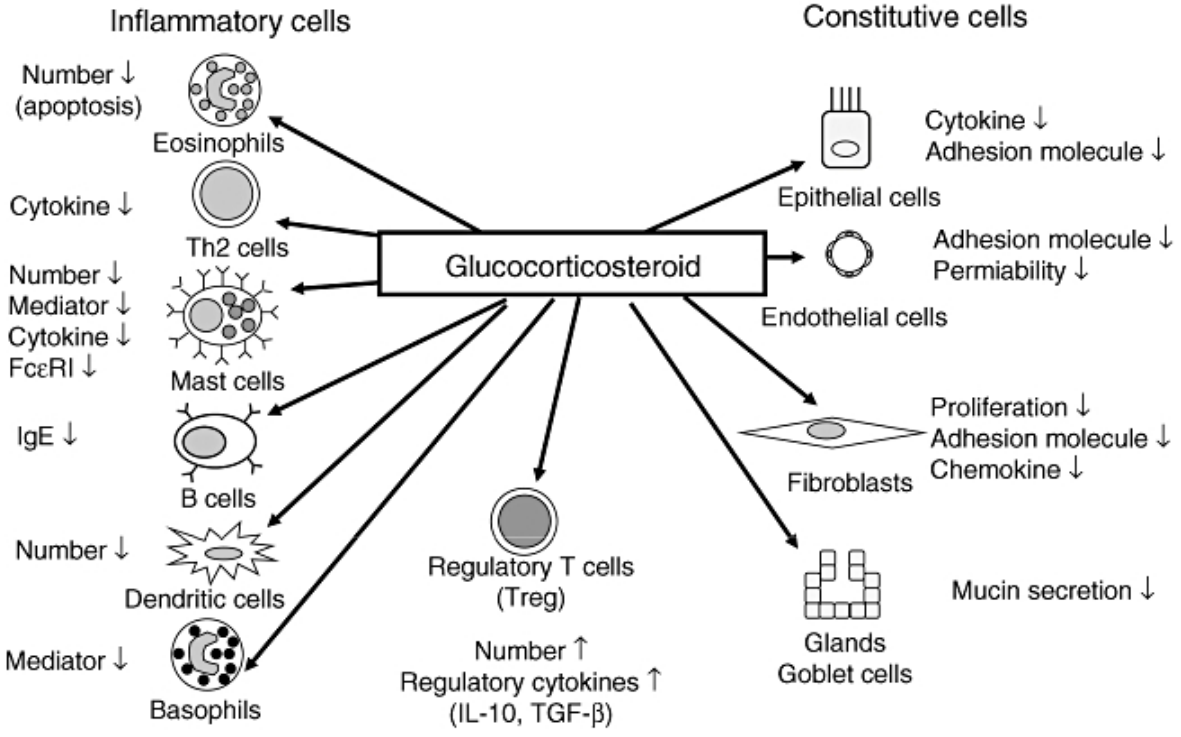
Molecular level

The action of the glucocorticoids(GC) begins at the molecular level when the glucocorticoid crosses the cell membrane and binds to the GC receptor. These receptors are present in the in the cytoplasm of the cell and are in an inactive form maintained by heat shock proteins. GC disrupts the heat shock proteins which enables the diffusion of GC into the nucleus of the cell. GC exerts its anti inflammatory response using two pathways. The first pathway is **transactivation** where in the receptor molecule which binds the GC encodes the anti inflammatory gene. The second pathway is by repressing the gene by **transcription** which inhibits the pro

inflammatory response of the cell(44).

Cellular level

GC inhibits the function of the infiltrating inflammatory cells into the nasal mucosa. GC also inhibits the cytokines and maturation of the mast cells. It inhibits the histamine release from basophils , enhances the apoptosis of eosinophils and reduces the recruitment of antigen presenting cells likethe Langerhans cells and dendritic cells. It also reduces the numbers of Th2 cells. It has also an anti inflammatory effect on nasal mucosal constituent cells such as epithelial cells, vascular endothelial cells and fibroblasts(45).



Doses

Intranasal steroids are better than any other drugs in the management of nasal block, congestion and rhinorrhoea. They exhibit their anti inflammatory effect by inhibiting the local infiltration of the effector cells of allergic inflammation. They also inhibit the

production and release of cytokines. They decrease the vascular permeability and down regulate the secretion of the mucous glands. Their onset of action is slow and the maximum efficacy develops over weeks and days. In extreme congestion, nasal steroid will not reach the mucosa and hence a decongestant is used initially and the steroid is used after that(46). Topical steroids can be used regularly and the usage can be commenced before the onset of pollen season.

Fluticasone propionate, beclomethasone, mometasone and budesonide are the most commonly used nasal steroidal sprays used. Fluticasone propionate contains 50 mcg per spray and the maximum dosage that can be given is 200mcg. Fluticasone furoate contains 27.5 mcg per spray and the maximum dosage to be given is 110mcg per day. Beclomethasone contains 42 mcg per spray and a total dose of 168 mcg per day can be given. Mometasone contains 100mcg per spray and a maximum of 400mcg can be given per day. Nasal sprays are administered into each nostril at regular intervals as once daily or twice daily doses.

Side effects

Intra nasal steroids can cause drying of the nose, crusting and resultant epistaxis. Fluticasone causes a decrease in the endogenous secretion of cortisol but there is no effect on adrenal suppression. Few studies show that there is a minimal decrease in the skeletal growth. Sivametal performed a randomized double blinded placebo controlled parallel clinical trial in 17 patients who had symptoms of impaired olfaction. The subjects received MometasoneFuroate or placebo for 2 weeks. Nasal peak inspiratory flow, chemosensory quality of life and olfactory function were assessed before and after

treatment. Nasal cytology samples were obtained from each visit and the biopsy specimen of the olfactory epithelium was obtained at the end of the study and was scored for inflammation. The results of this study showed that the patients on Mometasonefuroate had improved quality of life, olfaction, nasal symptoms and inflammation. Histological analysis of the olfactory epithelium showed that there were fewer eosinophils in patients who received Mometasonefuroate(29). Julliossonsetal performed a double blinded placebo controlled study of 25 patients with allergic rhinitis who were administered a 4 week treatment of topical fluticasone. The authors also studied the relationship between the tissue density of mast cells, tissue histamine levels and levels of markers of mast cell activation after an allergen challenge of the nasal mucosa in these patients following therapy with fluticasone. . Nasal biopsies were obtained before and after treatment. Mast cell density, tryptase levels and tissue histamine levels were evaluated. At 2 weeks intervals nasal challenges were performed for 8 weeks. The symptoms of nasal allergy were assessed after each challenge. Treatment with fluticasone propionate did not influence mast cell density or tissue histamine concentration. However, there was a reduction in nasal symptoms and tryptase in nasal lavage. This study showed that measurement of tryptase is an indicator of both mast cell activation and efficacy of topical steroid treatment(47).

LEUKOTRIENE ANTAGONISTS

Leukotriene antagonists act by inhibitingcysteinyl leukotrienes which are the important mediators of allergic rhinitis. There are two drugs which come under this cateogory, montelekast and zafirleukast. These 2 drugs are potent antagonists of type 1

cysteinyl leukotriene receptors(48).

Mechanism of action

Cysteinyl leukotrienes (C4,D4 andE4)cause increased microvascular permeability, inflammatory cell chemotaxis, mucus secretion and neuronal stimulation and bronchoconstriction. Compared to histamine, leukotrienes C4 and D4 are 1000 times more potent as bronchoconstrictors. These drugs are used often singly or in combination with antihistamines in the therapy of allergic rhinitis.

These drugs are well absorbed orally, highly plasma protein bound and metabolized by hepatic enzymes like CYP 2C9. The plasma half life of monteleukast is 3-6 hours(49).

Side effects

These drugs have few side effects, like headache and rashes.

Mast cell stabilisers

Sodium cromoglycate

This is a synthetic chromone derivative and inhibits the degranuation of the mast cell. Release of mediators from mast cell is prevented(50).. Long term treatment reduces the cellular inflammatory response. Sodium cromoglycate is not absorbed orally. It is administered as an aerosol. It is not a nasal decongestant. But regular usage as a prophylactic can produce symptomatic improvement in patients.

Effect of treatment of allergy on olfaction

The medical treatment of Allergic Rhinitis includes predominantly intranasal corticosteroids , antihistamines and leukotriene antagonists. Corticosteroids have a wide range of propertis. Their anti inflammatory property is used in the treatment of

Allergic Rhinitis. At the local site they cause membrane stabilisation and alteration in the release of mediators and inhibits the migration of cells. This mechanism is helpful in the restoration of the olfactory functiom at the olfactory mucosa. The advantage of using a steroid nasal spray is that high drug concentration is provided at the target receptor site and there is a minimum risk of side effects. Wober etal assessed the effect of azelastine in 211 children less than 13 years of age. These childern were treated with Azelastine nasal spary for 2 weeks. There was a significant reduction in the symptoms of these children who were treated with sprays. The olfaction has significantly improved from 72.1% to 94.6%(51). Gamberdella etal has compared in a randomized control study the effect of loratidine tablet with azelastine nasal spray. They have not found a statistically significant difference in the olfactory function of the patients in both the groups. Meltzer etal assessed the eefcet of treatment with mometasone on 41 individuals for 2 weeks. Olfactory fucnction was assessed with CCCRC test pre and post treatment. They have found that there was a significant increase in the odour threshold for the patients when treated with mometasone when compared to that with placebo(52). In a recent trial of Higaki etal in 2012, have studied the effect of 12 weeks of mometasone versus 4 weeks of placebo and 8 weeks of mometasone, and 12 weeks of placebo during the pollen season. Interstingly, they have found that there was no significant change in the three groups with respect to olfactory function(53)

Materials and methods

Study Design:

This is an observational prospective study

Study Population:

All patients who report to the ENT OPD who fit into the ARIA criteria of allergic rhinitis.

Inclusion Criteria:

- All patients diagnosed with allergic rhinitis
- Patients aged 18 years or greater
- Patients should not have used steroidal nasal sprays at least 2 weeks prior to the first test
- Patients without degenerative disease, neurological conditions or malignancy or recent nasal surgery

Exclusion Criteria

- Patients below the age of 18 years
- Patients who has obvious nasal pathology like sinonasal polyps, Gross deviated nasal septum which is touching the lateral wall of the nose and malignancy
- Patients with neurodegenerative disorders
- Patients with previous history of nasal surgery

Study Period:

This is a prospective study and was conducted between October 2014 to May 2016.

Ethics Committee Approval:

Once the study proposal was made, it was put forward to the Institutional Research Board. After obtaining the approval from the ethics committee, the study was initiated in November 2014.

Statistics

Sample Size Calculation

Sample size calculation was made based on a study conducted by Cowart etal in 1993 where in they studied the prevalence of patients with olfactory dysfunction in allergic rhinitis. In this study, they have recruited 91 patients with symptoms of allergic rhinitis and 80 normal individuals. A smell test was performed on all these patients. A percentage of 21.3% was calculated. The formula used the calculate sample size was :

$$\frac{n=4p(1-p)}{d2}$$

$$\frac{4*0.23*0.77}{0.5*0.5} = 272$$

Where p is the prevalence and d is the precision

Prospective Study Recruitment:

All patients who presented to our OPD with ARIA criteria of Allergic Rhinitis were

recruited in the study. A detailed history and anterior rhinoscopy is performed on these patients. Any patient with gross deviated nasal septum on anterior rhinoscopy, who had a nasal surgery in the past and who had any malignancy were not included in the study. IgE and Skin allergy test were performed on these patients. Allergen Skin testing is performed with different panels of common Allergens. A positive and negative control is measured and the test is interpreted accordingly. A CCCRC (Connecticut Chemosensory Clinical Research Centre) test is performed on all the recruited patients. This test consists of three scores which includes Odour threshold, Odour Identification and Odourdiscrrimantion. A composite score is obtained and the patients are divided into various groups of hyposmia.

Quality of Life is assessed using RQLQ questionnaire. The questionnaire used in this study is a validated questionnaire and it is used with the copyright permission of Professor Juniper. A detailed questions are asked to the patient in a language which they can understand in 7 different domains which includes limitation of activities, sleep, non nasal symptoms, practical symptoms, nasal symptoms, eye and emotional symptoms. The minimum composite score is 0 and the maximum score is 7. The mean of all these domains is calculated and there quality of life is assessed.

All these patients are administered steroid nasal spray with or without antihistamines and leukotriene antagonists for 8-12 weeks. Those patients who had moderate to severe hyposmia were followed up using the same test and the patients who had mild to normal hyposmia were followed up either through telephone or email for the assessment of quality of life post treatment.

Statistical Analysis

The data is analysed using SPSS 16.0 software and MS Excel. The Frequency tables are used for presenting all categorical variables and mean, SD and range were used to present the continuous variables. The histogram plot, barchart and piechart were used for the graphical representation. The association analysis was performed using Pearson Chisquare test. Pre-post analysis was performed using McNemar's test for categorical variables and Paired t test for continuous variables. The error plot were used for the graphical comparison of continuous variables. $p<0.05$ was considered statistically significant.

Data Analysis and Results

A total of 150 patients who satisfied the diagnostic criteria as per the study protocol were studied. Ten patients who were lost to follow up were excluded from the follow up analysis.

Gender Distribution (Table 1)

There were more men than women in this cohort. These figures could be attributed to the fact that men seek medical attention earlier than women.

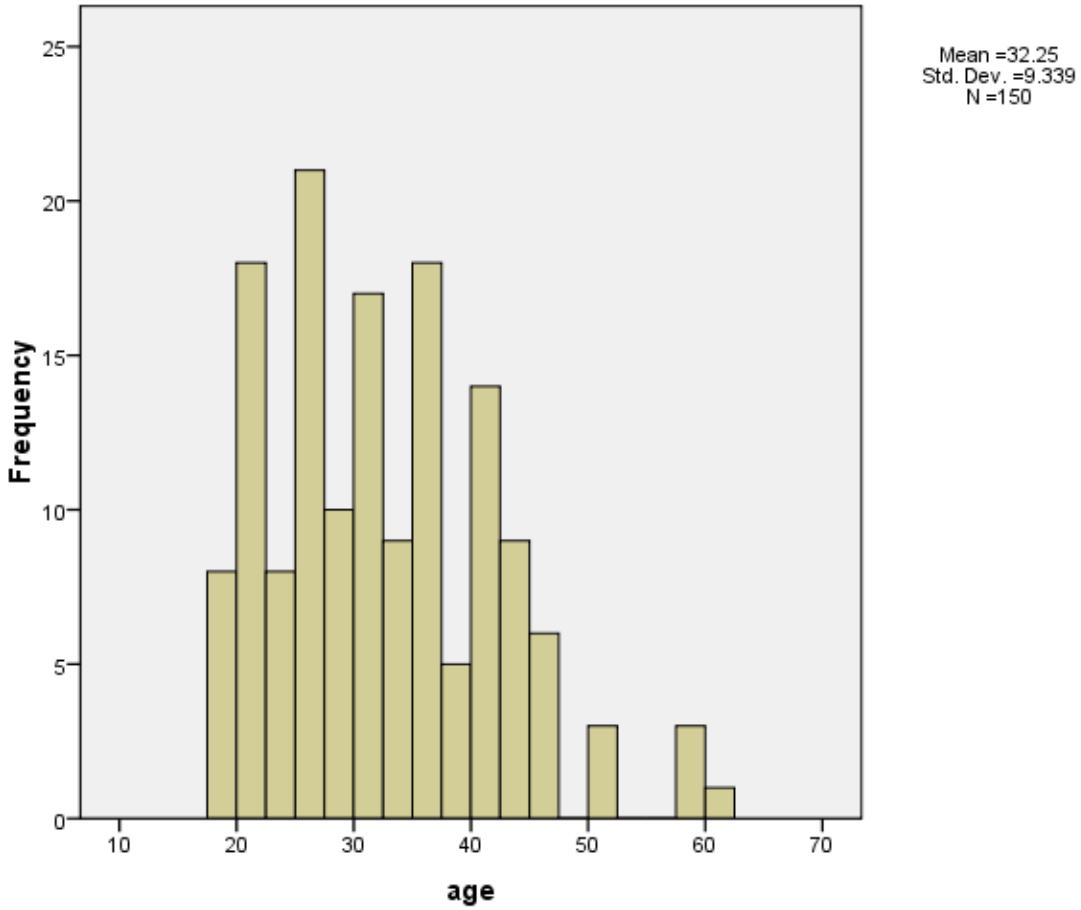
Table 1: Gender distribution(n=150)

Gender	**Number (%)**
Male	84 (56)
Female	66 (44)

Age distribution (Fig. 1)

Patient's ages ranged from 18-60 years (mean =32. 3 years; SD=9.4). Most (93%) patients were less than 45 years of age.

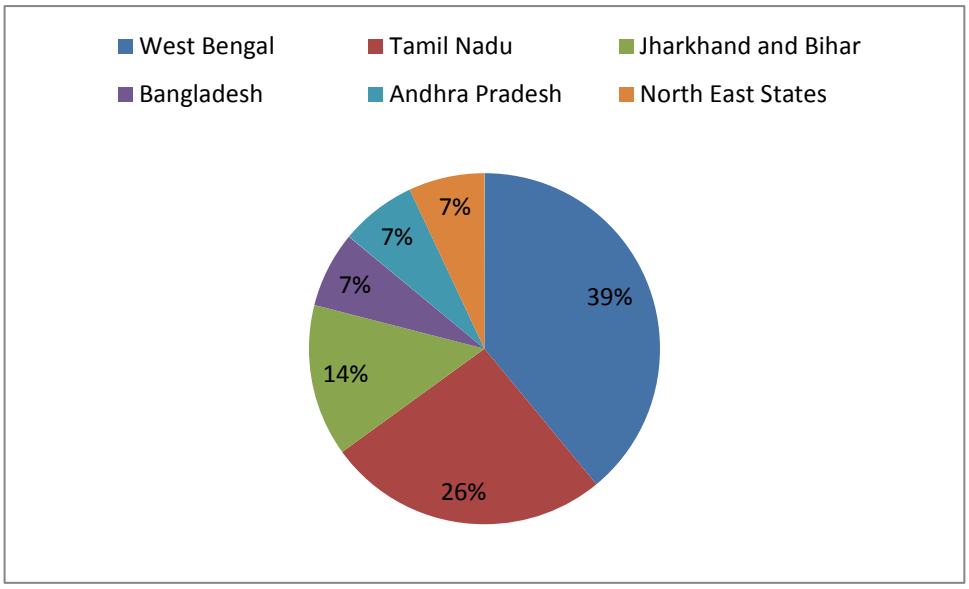
Fig 1. Age distribution of the study population



Geographical distribution (Fig. 2)

Most patients were from West Bengal (39%) or Tamil Nadu(26%)

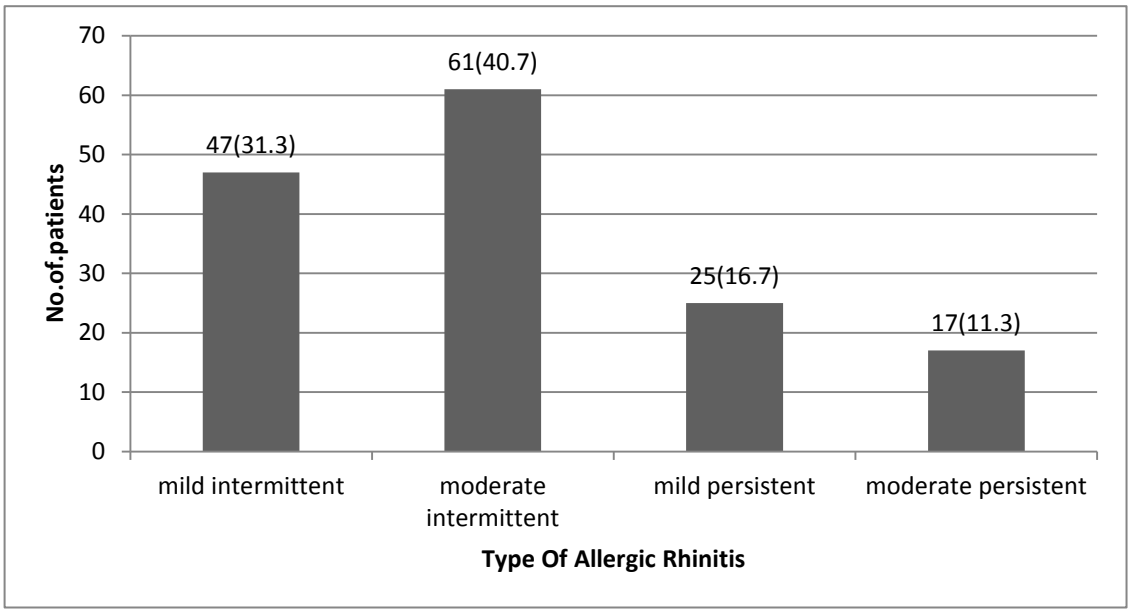
. **Fig 2. Geographical distribution of patients by State**



Distribution of types of allergic rhinitis (Fig. 3)

Based on the ARIA classification, the majority of patients (40.7%) had moderate, intermittent allergic rhinitis. Intermittent rhinitis (seasonal) (72%)was more common than persistent rhinitis (28%).

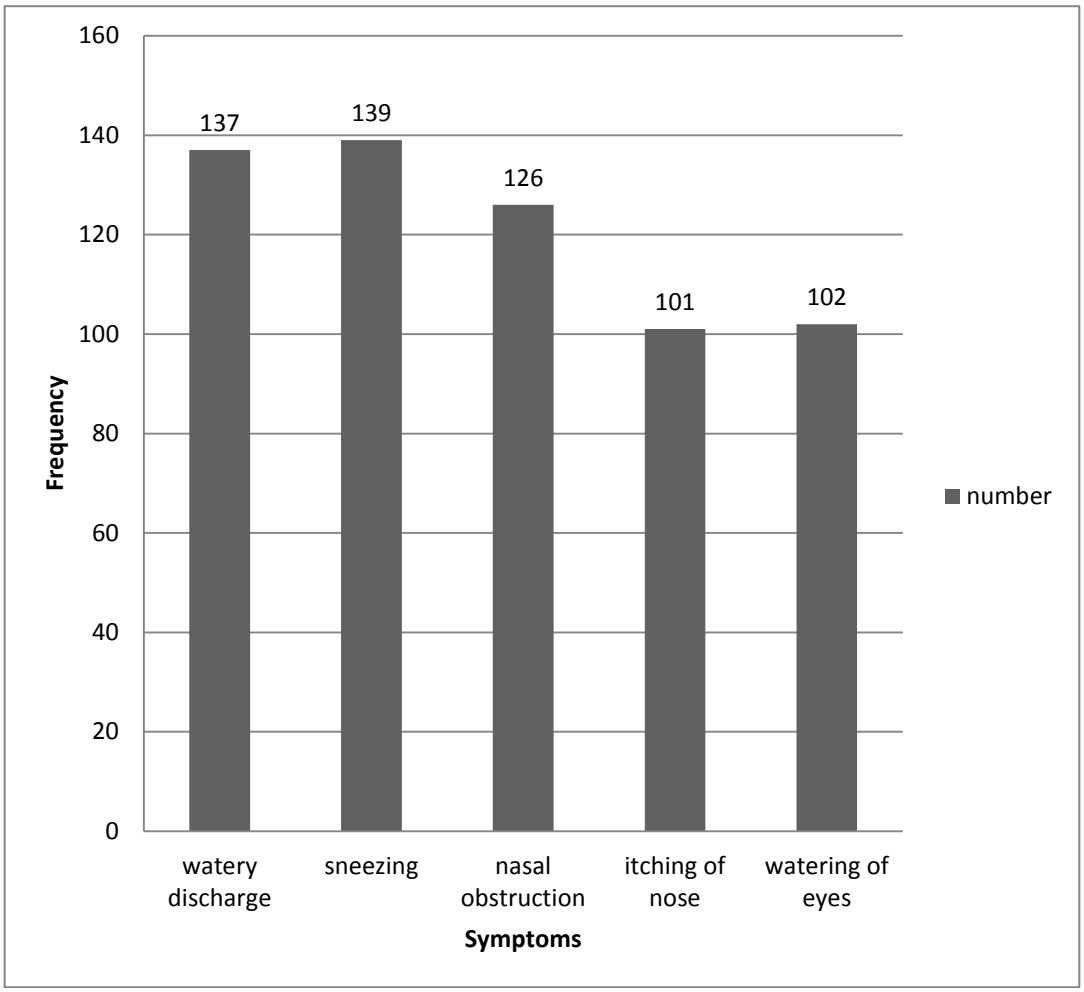
Fig 3 Distribution of types of allergic rhinitis



Symptoms

The most common symptom was watery nasal discharge and sneezing. Ocular symptoms were also frequently experienced (68%), although less than nasal symptoms.

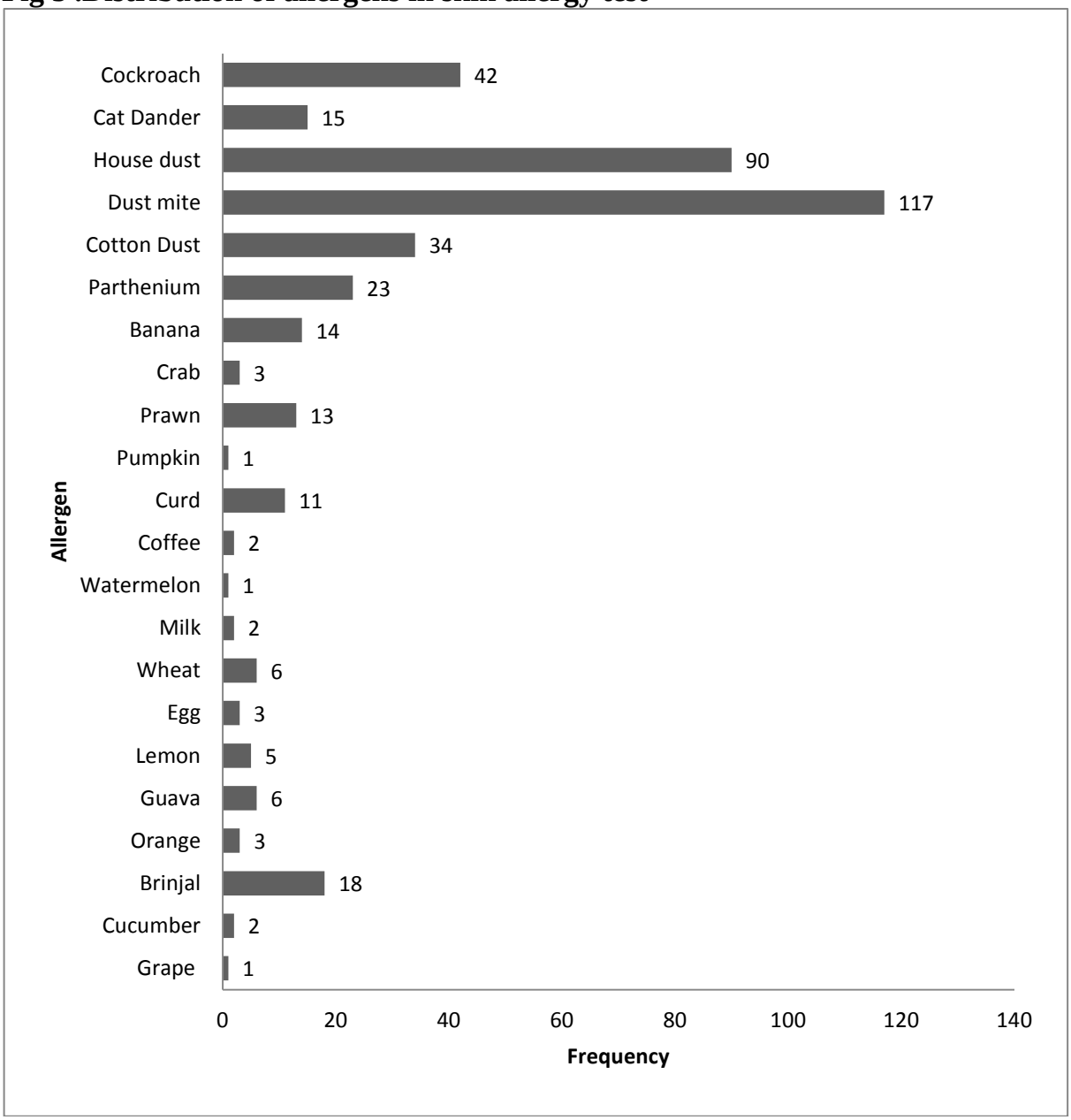
Fig 4 Symptomatology in allergic rhinitis



Skin allergy tests

Skin allergy tests were done to ascertain the various allergens that a particular patient was allergic to. Dust mite allergy was by far the commonest allergen (78%). House dust and cockroach were the next most commonly encountered allergens. Ingested allergens were much less frequently seen. The commonest ingested allergen was brinjal (12%).

Fig 5 .Distribution of allergens in skin allergy test



Smoking (Tables 2 , 3 and 4)

In this cohort, a little over half the patients (54%) appeared to have a smoking habit.

Smokers were more likely to have moderate to severe type of allergic rhinitis.

Table 2. Prevalence of smoking in cohort (n=150)

	Number (%)
Present	81 (54)
Absent	69 (46)
Total	150

Table 3. Severity of allergic rhinitis in smokers

	Mild(percentage)	Moderate(percentage)	Total	p
Smokers	29(35.8)	52(64.2)	81(100)	0.01
Non smokers	43(62.3)	26(37.7)	69 (100)	
Total	72	78	150	

Table 4. Type of Allergic Rhinitis in smokers

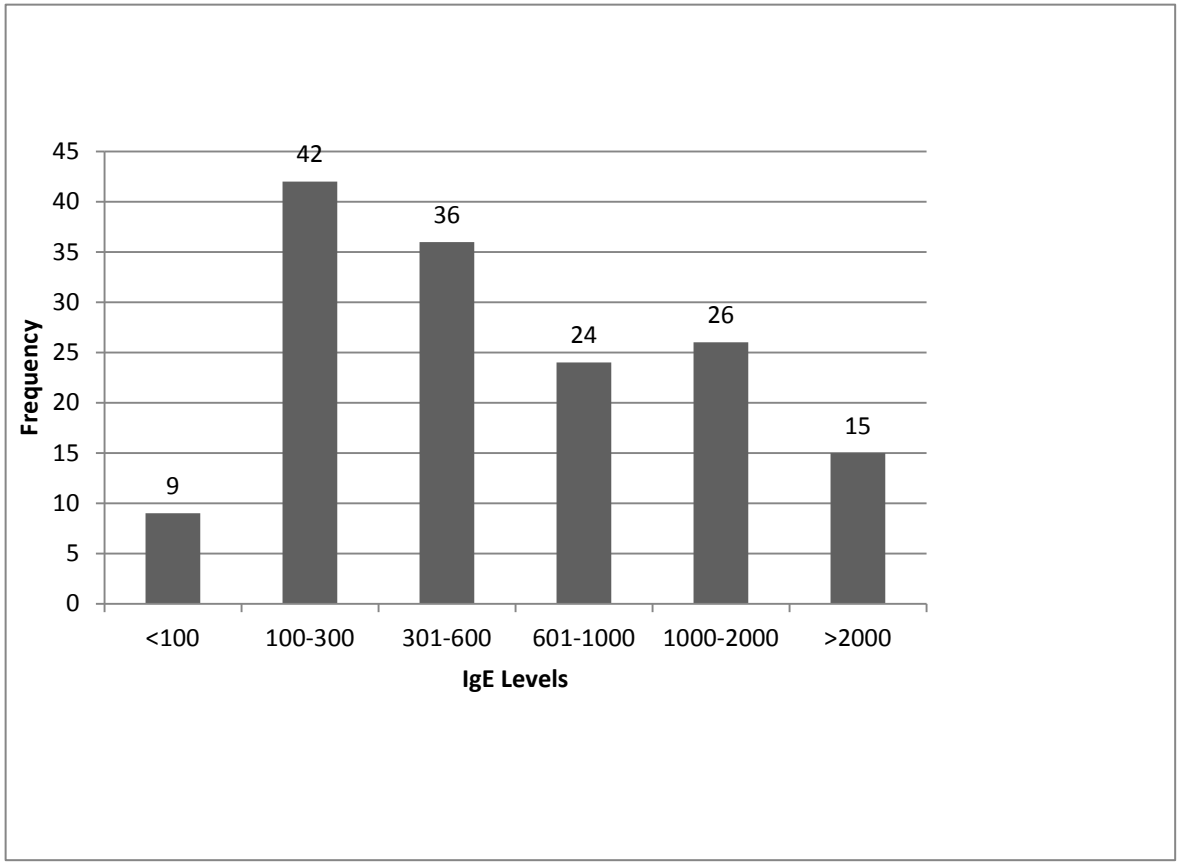
	Intermittent (percentage)	Persistent (percentage)	Total	p
Smokers	60(74.1)	48(25.9)	81(100)	0.33
Non smokers	21(69.6)	21(30.4)	69 (100)	
Total	72	78	150	

In this cohort smoking habit has no effect on the type of rhinitis, however has effect on the severity of rhinitis

Ig E levels (Fig.7)

Ig E levels ranged from 11.1 to 3000 U/l (mean = 737.47+/- 786.25)

Fig.6 Range of Ig E levels



Olfaction disturbances in patients with allergic rhinitis

Hyposmia was seen in 60% of patients with allergic rhinitis. Mild hyposmia was seen in (53.8%) of normal individuals too.

Olfaction scores (Tables 5 & 6)

Most patients had almost equal scores between nostrils in those with normosmia and hyposmia. In moderate to severe hyposmia this symmetry was not seen. Composite scores revealed that most patients (71.3%) had either normosmia or mild hyposmia.

Table 5. Distribution of olfaction scores (n=150)

	Left	Right
Normosmia(5.5-7)	64	66
Mild Hyposmia(3.75-5.4)	49	50
Moderate Hyposmia(2.5-3.74)	14	20
Severe Hyposmia(1.75-2.24)	20	10
Anosmia(less than 1.75)	3	4

Table 6.Seasonal Variations of Hyposmia

	Winter(percentage)	Summer(percentage)	Total	p
Normosmia	26(17.33)	81(54)	107(71.3)	0.001
Hyposmia	23(15.33)	20(13.33)	43(28.67)	
Total	49	101	150	

There is a significant seasonal variation in hyposmia in patients during winters when compared to summer.

Tab 7. Olfactory dysfunction vs type of allergic rhinitis

	Intermittent (percentage)	Persistent (percentage)
Normal	44(73.3)	16(26.7)
Mild	33(70.2)	14(29.8)
Moderate	9(50)	9(50)
Severe	17(89.5)	2(10.5)
Anosmia	5(83.3)	1(16.1)
Total	108(72)	42(28)

Tab.8 Hyposmia vs Type of rhinitis: Test of significance

	Intermittent	Persistent	Total	p
Normosmia	77	30	107	0.578
Hyposmia	31	12	43	
Total	108	42	150	

There is no statistically significant difference in hyposmia in patients with intermittent or persistent rhinitis.

Tab 9. Hyposmia vs severity of rhinitis. Test of significance

	Mild Rhinitis	Moderately severe rhinits	Total	p
Normosmia	55	52	107	
Hyposmia	17	26	43	0.041
Total	72	78	150	

Hyposmia is more prevalent in patients with moderate to severe type of allergic rhinitis. There is significant correlation between the severity of the disease with hyposmia.

Table 10. Olfactory score vs Severity of allergic rhinitis

	Mild (percentage)	Moderate(percentage)
Normal	35(58.3)	25(41.7)
Mild	20(42.6)	27(57.4)
Moderate	8(44.4)	10(55.6)
Severe	8(42.1)	11(57.9)
Anosmia	1(16.7)	5(83.3)
Total	72(48)	78(52)

When combinedolfactory scores were compared between 150 patients with normal to mildhyposmiaand moderate to severe hyposmia at the commencement of therapy, it was found that there was significant hyposmia in moderate to severe allergic rhinitis and the difference was statistically significant

Table 11. Compositeolfaction score prior to commencement of therapy

	Number(%)
Normosmia(5.5-7)	60(40)
Mild Hyposmia(3.75-5.4)	47(31.3)
Moderate Hyposmia(2.5-3.74)	18(12)
Severe Hyposmia(1.75-2.24)	19(12.7)
Anosmia(less than 1.75)	6(4)
	150

Post – treatment follow up

All recruited patients received 8- 12 weeks of medical therapy which included steroid nasal sprays, antihistamines and leukotriene antagonists in various combinations for a period of 3 months. These patients were followed up and the olfaction test repeated . A total of 34 patients who showed disturbances in olfaction prior to commencing therapy were found to have normal or mild hyposmia following completion of therapy.

Table 12.Severity of olfaction disturbances prior to therapy in the 34 patients who were followed up

	Frequency(%)
Normosmia	4(11.8)
Mild hyposmia	18(52.9)
Moderate hyposmia	12(35.3)
Total	34

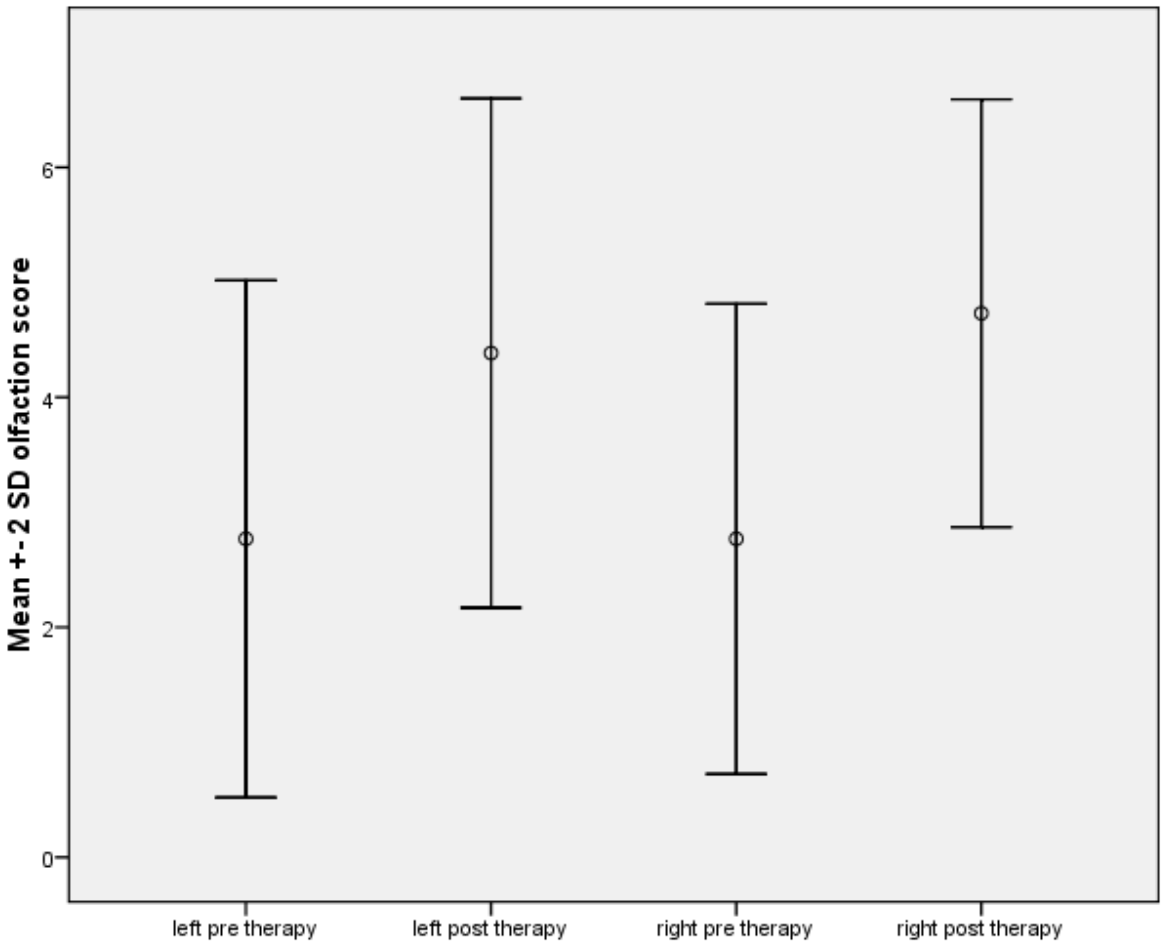
Following therapy, there was no patient with severe hyposmia or moderate hyposmia. Although the number of patients who had normosmia following therapy was low, there was certainly an improvement in the olfaction of the patients overall.

Table 13.Change in olfaction scores before and after allergy therapy

	Post therapy normosmia	Post therapy hyposmia	Total	p
Pre therapy normosmia	6	2	8	0.001
Pre therapy hyposmia	16	10	26	
Total	22	12	34	

Fig 7.The shift in the mean of olfaction scores pre and post therapy

When composite olfaction scores were compared before and after therapy in 34 patients in whom follow up was available, it was found that there was a significant improvement in mean scores and the difference was statistically significant (P=0.001).



Quality of life in patients with allergic rhinitis (Table 10)

Patients with allergic rhinitis demonstrated significant quality of life abnormalities. The mean QOL scores were raised, particularly those affecting nasal, emotional and non-nasal symptoms

Table 14. Mean QOL scores prior to commencement of therapy (n=150)

	Mean	**Standard Deviation**
Activities	2.637	1.66
Sleep	1.89	1.74
Non nasal	2.85	1.46
Practical	2.78	1.84
Nasal	3.66	1.31
Eye	2.46	1.53
Emotional	3.3	1.73

Pre therapy the mean of the nasal symptoms is high followed by practical, daily activities and non nasal symptoms.

Table 15. QOL changes following therapy (n=139)

	Mean	**Standard Deviation**
Activities	1.76	0.82
Sleep	0.98	0.64
Non nasal	1.58	0.79
Practical	1.67	0.82
Nasal	1.48	0.50
Eye	0.77	0.44
Emotional	2.35	1.18

There is a significant improvement in the nasal symptoms after treatment for 4-8 weeks When QOL scores were compared before and after therapy in 139 patients in whom follow up was available, it was found that there was a significant improvement in mean scores and the difference was statistically significant (p =0.00)

Table 16.Mean QOL scores before and after therapy (n=139)

	Mean	S.D.	p
Pre- therapy QOL scores	2.8453	1.18327	
Post therapy QOL scores	1.5074	0.79981	0.00
Mean improvement	1.33787	0.99831	

Fig 8.The shift in the mean of QOL scores pre and post therapy

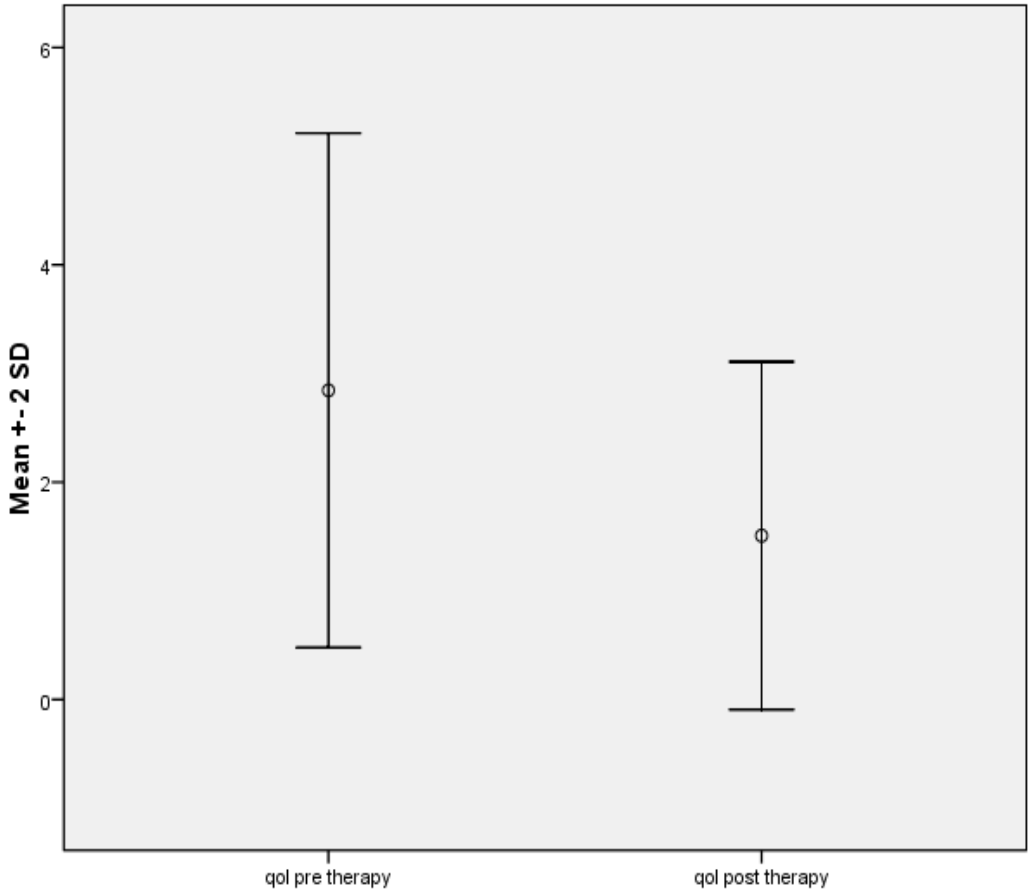
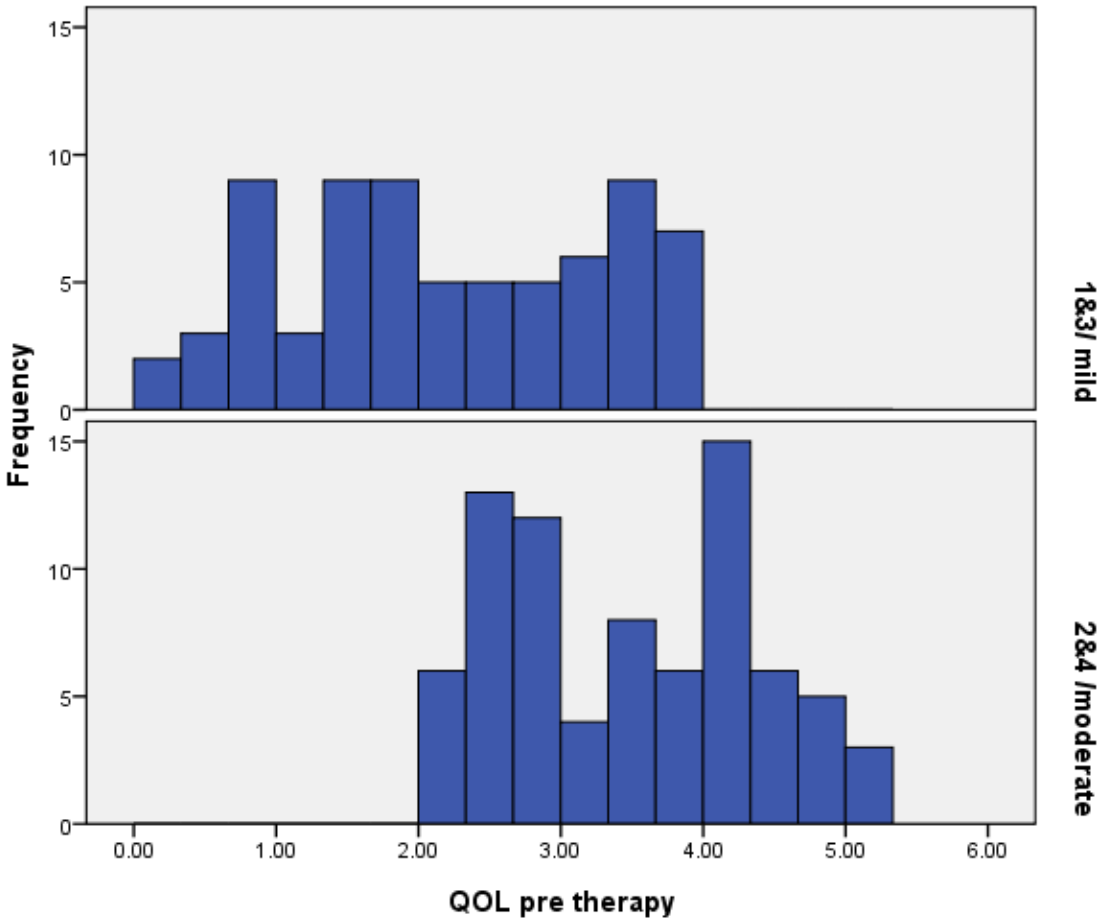
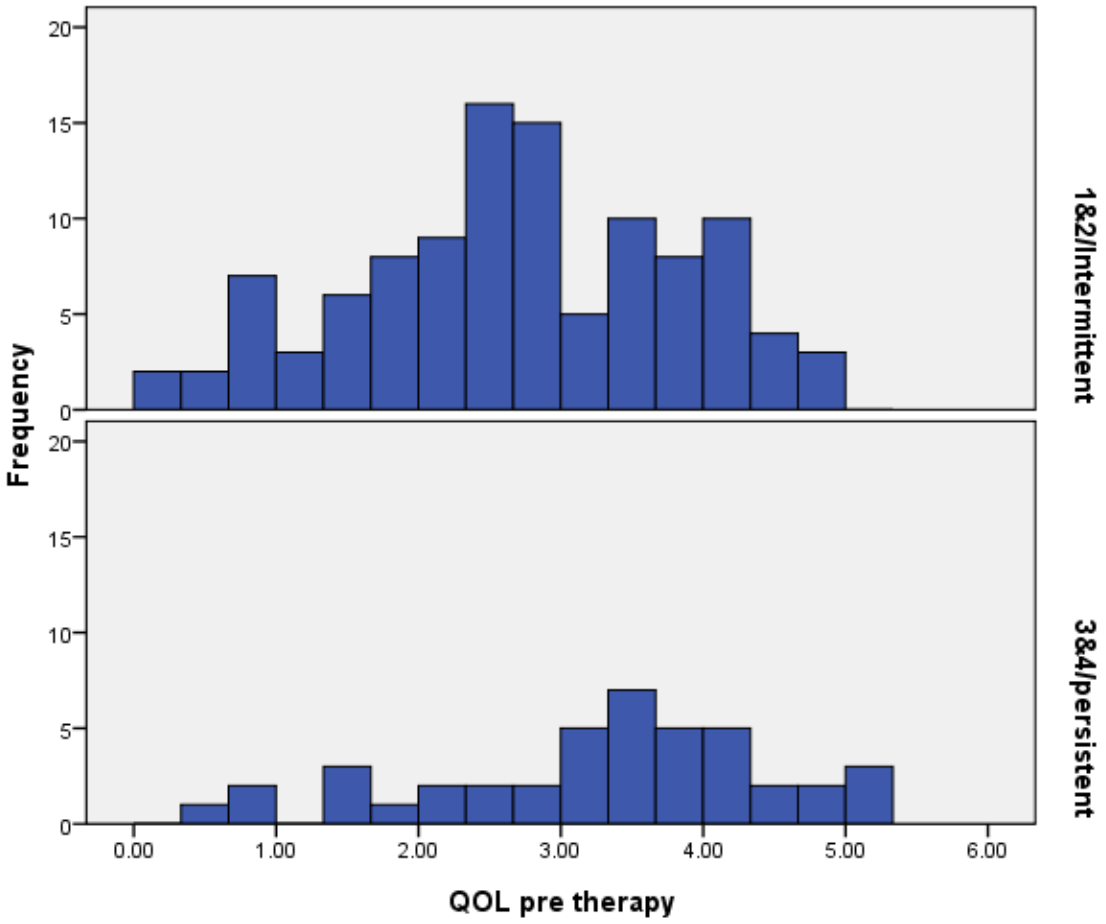


Fig 9 Quality of life in mild vs moderate to severe rhinitis



When QOL scores were compared between mild and moderate rhinitis in 150 patients at the time of recruitment, it was found that there was significant difference in mean scores of both the types of rhinitis(p=0.000)

Fig 10: Quality of life in intermittent vs persistent rhinitis



When QOL scores were compared between intermittent and persistent rhinitis in 150 patientsat the time of recruitment, it was found that there was no significant difference in mean scores of both the types of rhinitis(p=0.005)

Reduced QOL following therapy

Despite the overall improvement in quality of life, 9 patients were found to have reduced QOL scores following therapy. Analysis of this subset revealed that 5 patients had a posterior deviation of the nasal septum as seen in diagnostic nasal endoscopy. These patients had high nasal scores which persisted after treatment with steroid nasal spray and antihistamines for a period of 8 weeks. Four patients did not have any obvious anatomical abnormalities. In these 4 patients it was the non nasal, sleep and emotional domains that showed an increase in the score, thus affecting the overall score.

Discussion

Allergic Rhinitis, a condition which is characterised by persistent rhinorrhoea, itching and sneezing on exposure to a specific allergen or season is a common condition in our population affecting around 10%-30% of the world wide population (26) and 20%- 30% of the Indian population(54). The incidence of allergic rhinitis reported in Western countries is 1.4% to 39.7%(15). Olfaction is one of the important functions which is impaired in patients with allergic rhinitis. The loss of smell can be considered as a clinical marker in assessing the severity of allergic rhinitis(55). Among all the symptoms which a patient presents with in allergic rhinitis, hyposmia is the least investigated symptom. In our study we have studied the prevalence of olfactory dysfunction in patients with allergic rhinitis and the reversal of the same after treating with intranasal steroids and antihistamines. We have found in our study that 60% of patients who were diagnosed to have allergic rhinitis had olfactory dysfunction. Cowart et al(25), found that olfactory dysfunction was present in 23.1% of patients with allergic rhinitis. Guilemany et al(28) performed the Barcelona smell test in patients with allergic rhinitis and found that smell disturbances are presented in 21% - 23% of individuals. Becker et al (27) studied olfactory dysfunction in seasonal and perennial allergic rhinitis using the sniffin sticks test and found that these patients had impaired olfactory function when compared to the control group. There are not many Indian studies which have looked at the prevalence of olfactory dysfunction in patients with allergic rhinitisAnd our study is one of those studies which has attempted to address the issue.

Intranasal corticosteroids and antihistamines remain the mainstay of treatment of allergic rhinitis. Corticosteroids have been used to treat anosmia in various sinonasal

conditions. However, the results of studies in which steroids have been administered for allergic rhinitis have shown contrasting results. In a prospective study, the efficacy of intranasal and oral steroids in improving the sense of smell in24 patients whose sense of smell was tested pre and post surgery was noted.(8) .. The author found that patients who received oral steroid were more likely to show resolution of hyposmia compared to those who received nasal steroid spray. Sivam et al (29) studied olfactory dysfunction and the reversal of the same in patients with seasonal allergic rhinitis. In a randomized, controlled, double blinded placebo controlled study, they administered mometasone furaote for 2 weeks and measured olfactory function before and after administration of steroids. The researchers found that there was no significant change in olfaction function before and after therapy. Heilman et al(56) studied olfactory function in patients with upper respiratory tract infection, obvious sinonasal diseases and idiopathic inflammatory diseases. Both intranasal and systemic steroids were administered to the patients and olfactory function was measured before and after therapy. The authors concluded that olfaction was improved both in patients who were given systemic steroids and in those who were given intranasal steroids. Alobid et al (31), studied the effect of oral and intranasal steroid on smell and nasal conditions in patients with nasal polyposis. The researchers administered both oral and intranasal steroids and found that there was a significant improvement in smell after treatment with a combination of oral and topical steroids.

Antihistamines are used as a primary modality of treatment for allergic rhinitis. Second generation antihistamines are more useful and have fewer side effects when compared to first generation antihistamines. In our study we used second generation

antihistamines for the management of all patients. Bachert et al (57) , in a systematic review of literature on the efficacy of antihistamines on allergic rhinitis and asthma, concluded that antihistamines attenuate the symptoms of early and late phase reactions of allergic rhinitis. Compaliti etal (58) performed a metaanalysis of randomized, double blinded, placebo controlled studies which evaluated the efficacy of fexofenadine. They found that fexofenadine is effective and safe in allergic rhinitis. Schaper etal (59) studied the efficacy of fexofenadine, a second generation antihistamine in patients with allergic rhinitis and found that it was effective in reducing the nasal and ocular symptoms of an individual. In our study we found that a combination of topical steroid and oral antihistamine significantly reduced hyposmia($p=0.001$). Our study has shown that intranasal steroids with antihistamines not only improve the allergic symptoms but also has a significant improvement on the olfactory function of the individual.

Allergic rhinitis is a common chronic disorder which has an overall impact on an individual's QOL. However, in a developing country like India, not much attention is given to QOL in allergic rhinitis, either by the patients themselves, the patient's family or health care professionals. Allergic rhinitis, despite its chronicity, is often treated like upper respiratory tract infection in many parts of the country(60). As a result, not much attention has been paid to the QOL in this condition.

A number of Western studies have looked at the impact of allergic rhinitis on QOL. Valero et al (61) studied the severity of allergic rhinitis and its impact on QOL in relation to the severity. They used a validated questionnaire ESPRINT for assessing QOL. They found that the worsening of QOL was proportional to the severity of allergic rhinitis. Katotomichaelkis et al (37)studied the impact of olfactory dysfunction on QOL

in patients with allergic rhinitis and in patients with chronic rhinosinusitis. Allergic rhinitis patients were treated with immunotherapy and those with chronic rhinosinusitis were treated with endoscopic sinus surgery. The authors concluded that improvement in olfaction had an impact on QOL in patients with allergic rhinitis($p= 0.004$) as well as those with chronic rhinosinusitis ($p<0.001$). These values are statistically significant. In our study we, too, have found that administration of medical therapy had a significant impact on QOL in patients with allergic rhinitis. The results of our study are consistent with the results in literature reviewed thus far. Shaw et al. (62) assessed QOL in Indian population with RQLQ questionnaire in 34 patients with allergic rhinitis. They concluded that the disease caused a significant impairment in emotional, practical and activity limitation and they were less troubled by lack of sleep. These symptoms improved after treatment for 4-8 weeks. In our study it was the nasal, non- nasal, practical, emotional and general limitation of activities which were affected. There was no significant impact on sleep. Post treatment there was improvement in all the symptoms in most patients. Nine patients showed reduction in QOL scores following therapy. In 5 of these patients QOL scores were persistently high even after medical therapy because of persistent nasal obstruction due a deviated nasal septum which was evident only with rigid nasal endoscopy. In another 4 patients, the emotional and non nasal symptoms continued to be prominent, necessitating further evaluation. These results suggest that is important to assess QOL also in these patients and not merely depend on the results of allergy evaluation in managing these patients. The results of our study also show that Indians do not consider sleep as an important aspect of QOL. This finding is similar to that noted by Sinha et al(18). Meltzer et al (63) conducted a

similar study to assess QOL using HRQL(Health Related Quality of Life) in adolescents with allergic rhinitis. The researchers concluded that there was significant impact on QOL in allergic rhinitis in this age group too. The QOL was affected by both nasal symptoms and activity limitation of patients and there was no significant impairment in sleep or non nasal components.

Surprisingly, there are no studies which mention the absence of improvement of QOL. However in our study, we found that QOL impairment could be persistent and could be secondary to emotional and non- nasal domains. Emotional domains seem to be more affected in women when compared to men.Canonica etal (64) conducted an online and telephone survey of patients with allergic rhinitis. They had 3635 responders from 6 different countries. The authors found that QOL was worse in spring time and that nasal symptoms were more severe. Similar results have been noted in animal studies which showed the variation of olfaction with change of season. In our study we found that the incidence of hyposmia during winters is higher compared to summer($p=0.001$). Tham et al (65) conducted a study on aeroallergen sensitivity in the Asian population and found that unlike in Western countries, pollen is not a common allergen in the Asian population. House dust mite happens to be the most common aeroallergen. Despite dust mite being the most common allergen which we have found in our study, intermittent rhinitis seems to be the most common type of allergic rhinitis in our study. Cuskon et al (66)found that dust mite is the most common type of allergen (84.4%) in both intermittent and persistent rhinitis. The reason behind this could be that in atopic individuals who are more sensitive to the seasonal variations of rhinitis, the sensitivity to other allergens is also high and they might not produce the severe clinical

expression of the allergic symptoms.

In the present study the most common type of allergic rhinitis found was intermittent rhinitis (72%). This is in contrast to another Indian study by Deb et al (24) who studied the clinical profile of patients with allergic rhinitis in West Bengal. The authors found that the most common type of rhinitis is persistent rhinitis. Our results were similar to the study by Valero et al (61)who found that the most common type of rhinitis was intermittent rhinitis (61.5%) Similarly, Becker et al (7)studied olfactory dysfunction in seasonal and persistent allergic rhinitis and compared it with a control group. In their study, they found that seasonal rhinitis is more common than persistent rhinitis.

The most common symptoms noted in our study were watery nasal discharge, sneezing and nasal obstruction. Ocular symptoms were noted in 68% of the individuals although they were still less frequent compared to nasal symptoms. Aidan et al (67)studying the various symptomatology of allergic rhinitis found that nasal congestion was the most common symptom when the patient wakes up early in the morning. However, most of the other studies showed that the most common symptoms in allergic rhinitis are watery nasal discharge, sneezing and nasal block(22),(15),(54).

Deb et al (68) in their study from West Bengal found that 64.7% of their study group was exposed to tobacco smoke. The authors, however, did not study the association between smoking and severity of allergic rhinitis. In our study we found that 54% of the cohort was exposed to tobacco smoke. Interestingly, although tobacco smoke has no effect on the type of rhinitis ($p=0.33$), there is a significant association with the severity of rhinitis($p=0.01$). Similarly, Sinha et al (62) who performed a community- based

study in Delhi, found that smoking had a significant effect on the severity of the allergic rhinitis. The authors also found that with the increase in the number of pack- years of smoking, the severity of the disease also increases. Alhough there was substance abuse in different forms in the cohort of patients studied, it did not show a significant effect on allergic rhinitis in comparison to the effect of smoking. Fernandes et al (69) performed a cross sectional study in adolescents to look at the association between early exposure to smoking and the development of allergic rhinitis. The authors found that there is a strong correlation between early exposure to smoking and the development of diseases like allergic rhinitis and asthma.

In conclusion, the results of our study shows that allergic rhinitis in the adult Indian population is mainly mild or moderate and intermittent rather than persistent. The disease is more severe in smokers and associated with mild to moderate hyposmia. Symptomatology is worse in the winter months. Allergic rhinitis significantly impacts quality of life and olfaction in affected individuals. There is reversal of both hyposmia as well as quality of life in those who receive medical therapy with inhaled steroid and antihistamines. In those with persistent symptoms, the presence of anatomical obstruction due to a deviated nasal septum or the presence of significant emotional or non-nasal symptoms should be evaluated carefully.

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Annexures

INFORMED CONSENT

Christian Medical College, Vellore
Department of Otorhinolaryngology

Study of olfactory disturbances and quality of life in patients with allergic rhinitis and the reversal of these parameters after medical therapy in affected patients

Information sheet

You are being requested to participate in a study. In this study we test your olfaction(ability to smell) using butanol test and also assess your quality of life using a quetionnaire. In this test you will be given a solution at different concentrations and you will be asked at which concentration can you identify the smell. You will also be asked to smell different odours and see if you can differentiate between the different odours and identify each odour.
If you are diagnosed with a condition called allergic rhinitis(recurrent episodes of sneezing on exposure to allergen) then you have to do this test before we start your treatment and after we complete your treatment.
We are hoping that your sense of smell will improve followed by our treatment.

What is butanol test and odour identification and odour discrimination

Butanol is butyl acohol(chemical) which is given at different dilutions and you are asked to smell the different concentrations and tell us at which concentration can u identify the smell. This test is repeated independently in each of the nostril. In odour identification and discrimination you are asked to smell different odours which we use in our daily life like coffee powder, cinnamon etc, and you are expected to identify each odor and differentiate it from the other one.

Does butanol test have any side effects?

There are no side effect for this test. This will just help us to identify the extent of your disability

If you take part what will you have to do?

As mentioned above you have to go through the butanol test and odour identification and odour discrimination test and your results will be documented pre and post therapy. You are requested to answer a few questions regarding your problem and about your quality of life.

Post therapy test will be done around 2-3 months after your treatment. All other treatments that you are already on will be continued and your regular treatment will not be changed during this study. No additional procedures or blood tests will be conducted routinely for this study. There is no extra cost which you have to pay for this study. If at any time you experience any problems, you will be expected to report this to the doctor. You will also be contacted by telephone at least once in between the monthly visits by the doctors in this study who will ask you about any side effects you are experiencing.

Can you withdraw from this study after it starts?

Your participation in this study is entirely voluntary and you are also free to decide to withdraw permission to participate in this study. If you do so, this will not affect your usual treatment at this hospital in any way.

What will happen if you develop any study related injury?

We do not expect any injury to happen to you but if you do develop any side effects or problems due to the study, these will be treated at no cost to you.

Will you have to pay for the test

You need not pay for the test. Any other treatment that you usually take will continue but the usual arrangements that you have with the hospital will decide how much you pay for this.

What happens after the study is over?

After the study is over, you will be able to see if your ability to smell has improved or not. And moreover this results will help us to quantify the problem in our population and we will be able to see the reversal of olfactory dysfunction in patients following treatment

Will your personal details be kept confidential?

The results of this study will be published in a medical journal but you will not be identified by name in any publication or presentation of results. However, your medical notes may be reviewed by people associated with the study, without your additional permission, should you decide to participate in this study.

If you have any further questions, please ask

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AA	sex	age /sex	ac 2	activities	sleep	non nasal	practical	nasal	eye	emotional	Allergen 1	Allergen 2	Allergen 3	Allergen	Allergei
olfar 1	2	22	0	0	0.66	2.57	0.66	1.75	0	0.25	11	13	14		
olfar 2	1	18		2	0	2.28	2	4	1.25	3	15	16	11		
olfar 3	2	21		4.67	1.33	2.57	6	5	4.25	5.25	2	1	9		
olfar 4	1	46		0	1.33	1.42	3.67	4.67	3.75	6	11	15	16		
olfar 5	2	40		1.33	0	0.85	0	2	0	0.25	11	12			
olfar 6	1	22		5.67	4.25	2.22	4	4.5	6	4.25	11	15	16	18	12
olfar 7	1	25		0	0.33	3	0	3.75	0.75	2.75	15	6			
olfar 8	1	27		2.33	3	2.14	5	2.75	6	5.5	15	11	16	1	19
olfar 9	1	18		3.34	1.33	4.44	5	5	5	4.75	15	16	18		
olfar 10	1	33		1	0	4.28	1	5.5	1.25	5	15	11			
olfar 11	1	20		0.67	0	1.57	3.67	4	0.75	5	15	16	17	19	2
olfar 12	2	22		4.67	3.67	5.28	4.25	2.75	4.75	5	11	15	16		
olfar 13	2	21		4.33	1	1.55	5.67	3.25	1.5	2.25	15	13	17		
olfar 14	2	21		4.67	3.33	3.42	3.33	2.75	1.75	3.5	15	11	17		
olfar 15	1	27		2.67	1.33	3.2	5	4.5	2.75	4	15	16	19		
olfar 16	2	26		3	1	3.42	6	5	4.5	5.25	15	11	13	20	
olfar 17	1	26		0.67	0.33	0.42	3.33	2.5	0.25	0.75	15	11	21	13	2
ofar 18	2	34		0	0	1.42	2	1	1.25	0.5	2				
olfar 19	1	30		1.67	0	3.71	0.33	2.5	2.25	2.25	15	11	18	19	
olfar 20	2	42		6	0	2.42	2.67	3	2.75	4.25	15	12	2		
olfar 21	1	18		0.67	0	1.71	4.67	3	1.75	0.25	15				
olfar 22	1	36		0	0	2.42	0.67	2	1	0	15	11	18	22	
olfar 23	1	34		1	0.67	0.57	1	1.33	4.67	0.25	12	15	16		
olfar 24	1	18		2	0	1.28	3.67	3.75	0	0	15	11	18		
olfar 25	1	35		0	0	5.2	3.67	2.75	3.67	3.75	15	2			
olfar 26	1	28		0	0	1.85	1.67	4.5	2.5	6	15				
olfar 27	1	26		4.33	3	3.71	4.33	5	4.5	4.5	2	11	22		
olfar 28	2	23		4.67	1.67	4.14	2	4.5	2.75	5.5	15	11	23	20	19
olfar 29	1	38		1.67	0.33	1.14	0.67	1.25	0.5	1.2	15	11	12		
olfar 30	1	19		1	0.33	3.28	2.33	4.25	4.5	4.25	15	11	16	18	
olfar 31	2	45		3	0	2.71	5.33	2.75	2	2.5	11	15	20		
olfar 32	2	37		0.67	1	0.55	0.67	3.67	1.75	4.25	18				
olfar 33	1	29		1.67	0	0.42	2	4.5	1.75	1.25	15				
olfar 34	1	28		6	4.25	5.14	6	5.5	5.25	3.25	15	11	18		
olfar 35	2	36		2	0	4.42	6	6	3	3	15	11	18	16	
olfar 36	2	40		2	2	1	2	3	0.5	1.75	15	11	16		
olfar 37	1	31		6	1.33	3.14	2.67	4	0	1.5	15	24			
olfar 38	2	32									12	16	18	2	
olfar39	2	22									15	11	18		
olfar 40	2	31		3.67	3	3.85	3.33	3.75	3.25	4.5	22	23			
olfar 41	2	37		4	3	3.85	3.33	3.5	3.5	4.25	15				
olfar 42	2	32		1.33	1.67	3.33	0.67	1.75	0.75	0.75	15	17			
olfar 43	1	28		2.67	1.33	2.42	5	3.75	2.5	4.75	15	15	23		
olfar 44	1	41		1	4	4.28	4	4.5	4.25	3.25	15	11	16	19	4
olfar 45	2	18		2.33	2	4.85	4.5	4.25	0.5	1.05	15	11	18		
olfar 46	1	41		3	1	2	0.67	4.25	2.75	2.75					
olfar 47	1	21		2	4	4.55	3.25	3.75	1	4	11	2	3		
olfar 48	2	37		3.25	3.75	4	3.33	4.25	2.5	3	15	11			
olfar 49	1	25		3.33	3.67	2.28	2.67	3.75	3	1.5	15	11	16	18	12
olfar 50	2	28		1.67	2.67	0.714	2.67	2.75	2.25	2.25	15	11	16		
olfar 51	2	42		1.33	1.33	1.14	3	3.25	0.75	4	16	2			
olfar 52	2	26		4	6	2.85	2.33	3.5	4.5	5	15	11	16	12	
olfar 53	1	35		3.25	2.67	3.28	1.67	3.67	1.5	1.5	15	11			
olfar 54	2	25		0	0	0.57	1.33	0.75	0.25	1	15	2			
olfar 55	2	43		3	3	3.14	3.67	4.75	3.67	5	15				
olfar 56	1	27		1.67	0	0.71	1.33	1.5	0.25	0.75	15	11	16	17	
olfar 57	2	23		0.67	0.67	3.5	3.67	4.75	2	2.25	15	11	16	18	17
olfar 58	2	20		4.67	1.33	3.55	3.33	5.75	5.25	5.75	15	11	13		
olfar 59	1	21		0	0.33	0.85	0	0	0.25	0.25	15	11	3		
olfar 60	1	24		1	1.33	0.55	0.67	1.5	1.5	2	15	11	17		
olfar 61	1	31		0.33	0	0	1	2.5	1	0.5	15	11	16	18	4
olfar 62	1	33		5	1.33	4.42	2.33	4.5	4.75	4.25	15	11	18	23	22

State	Diagno	watery na	sneezing	nasal obs	nasal	waterin	smokir	IgE	Skin allerg	olfacti	olfactio	olfaction	sunil	my sco	qol pre th	olfactio	olfactio	scori	qol post
1	1	2	1	1	2	1	2	646.9	positive	2	5.5	6	1	1	0.84			1	0.33
2	4	1	1	1	2	1	2	538	positive	4	3	2.5	4	2	2.075			1	1.08
1	2	1	1	1	1	1	2	59.3	positive	2	5.5	1.5	5	3	4.15	6	4.5	1	0.45
6	2	1	1	1	1	1	2	130.1	positive	2	5.5	6	1	3	3.311			1	0.48
3	1	1	1	1	2	1	2	1012	positive	1	6	6	1	1	0.63	4.5	5	1	0.55
3	2	1	1	1	2	1	2	2176	positive	4	2	3	4	3	4.41			1	
2	1	1	1	1	1	1	2	1284	positive	4	2	2	4	1	0.975	3	5	1	
2	2	1	1	1	1	1	2	237.3	positive	3	4	5	2	3	3.81	6	6	1	0.97
2	2	1	1	1	1	1	2	234.7	positive	5	1	1	5	3	4.23				
1	1	1	1	1	1	1	1	230.2	positive	2	5	4	3	2	2.57			1	
3	1	1	1	1	1	1	2	511.3	positive	1	6	5.5	2	2	2.23			1	1.08
1	2	1	1	1	1	1	2	570.8	positive	4	3.5	3	4	3	4.338	6	6	1	1.22
1	1	1	1	1	1	1	2	549.1	positive	4	2	3.5	4	2	2.792	5	5	1	1.08
1	3	1	1	1	1	1	2	165.7	positive	2	5	5.5	2	3	3.25			1	1.03
2	3	1	1	1	1	1	2	113.8	positive	1	6.7	7	1	3	3.35			2	2.95
2	4	1	1	1	2	1	2	110.4	positive	4	3.5	4	3	3	4.02	3	3	1	0.19
1	1	1	1	1	1	2	2	159	positive	4	2	3	4	2	1.702	4.5	5	1	0.23
3	3	1	1	1	1	2	2	384	positive	2	5	5	2	1	0.88			1	0.65
6	3	1	1	1	1	1	2	677	positive	1	6.6	7	1	2	1.81			1	0.54
4	2	1	1	1	1	1	2	238.5	positive	2	5.5	6	1	3	3.01			2	1.34
3	1	1	1	1	1	1	2	420.3	positive	2	5.5	5.5	2	2	1.72			1	0.84
3	1	1	1	1	2	1	2	382.5	positive	2	5	6	1	1	0.87			1	0.78
1	3	1	1	1	1	1	2	1078	positive	2	5	3	4	1	1.35	6	6	1	0.83
1	3	2	1	1	2	2	2	1021	poitive	2	5.5	5.5	2	2	1.52			1	0.93
3	2	1	1	1	1	1	1	721	positive	1	6	6	1	2	2.87			2	1.53
3	4	1	1	1	2	2	1	1109	positive	4	2	1	5	2	2.36	5	5	2	2.07
3	4	1	1	1	2	2	1	1092	positive	2	5.5	5.5	2	3	4.19	5	5	2	2.5
1	3	1	1	2	2	2	1	1139	positive	3	4	3.5	4	3	3.604	5	5	2	1.32
2	1	2	1	1	2	2	2	449	positive	2	5.5	5.5	2	1	0.965			1	0.89
4	2	1	1	1	1	1	1	380.6	positive	1	6	5	2	2	2.848			2	1.7
1	2	1	1	1	2	2	2	180.4	positive	1	6	5	2	2	2.612			1	0.88
3	1	1	1	1	1	1	2	577.4	positive	2	5	5	2	2	1.794			2	1.81
3	1	1	1	1	2	2	2	759.8	positive	2	5	6	1	2	1.655			2	1.4
3	4	1	1	1	1	1	1	1098	positive	1	6.5	6	1	4	5.055			3	3.03
3	3	1	1	1	1	1	1	230.7	positive	1	6	6	1	3	3.48			2	1.45
2	1	1	1	1	2	2	2	191	positive	1	6	6	1	2	1.75			2	1.53
3	1	1	1	1	2	2	2	235.4	positive	1	6	6	1	2	2.662			2	1.73
1	2	1	1	2	1	1	1	130	positive	2	5.5	6	1	2	2.22			1	0.83
3	2	1	1	1	1	1	2	986.4	positive	2	5.5	6	1	2	2.14			2	1.63
2	1	1	1	1	1	1	1	339.2	positive	2	5.5	5.5	2	3	3.58			1	1.81
3	2	1	1	1	1	1	1	234.8	positive	1	6.5	6	1	3	3.632			2	2.36
3	3	1	1	1	2	2	2	112.7	positive	1	6.5	6.5	1	1	1.464			1	0.87
3	4	1	1	1	1	1	1	328.6	positive	2	5	5	2	3	3.2			2	2.71
3	1	1	1	1	1	1	1	257.8	positive	2	5.5	5.5	2	3	3.04			1	0.96
2	2	1	1	1	2	2	1	699.8	positive	1	6	6.5	1	2	2.78			2	2.87
3	1	1	2	1	1	1	2	159	positive	2	5.5	6	1	2	2.34	5	5	2	2.78
1	1	1	1	1	2	2	2	2780	positive	5	1.5	5	2	3	3.22	3	5	2	1.53
3	2	1	1	1	1	1	1	488.5	positive	5	1.5	4	3	3	3.44	3	5	2	2.78
3	2	1	1	1	1	1	1	826.7	positive	2	5.5	6	1	2	2.885			2	2.34
3	1	1	1	1	1	1	1	735.3	positive	1	6	6	1	2	2.14			1	1.04
3	1	1	1	2	1	1	1	239.1	positive	1	6	6	1	2	2.114			1	1.46
5	2	1	1	1	1	1	1	751.8	positive	3	4.5	5	2	3	4.02	3	6	2	2.53
1	3	1	1	2	1	1	2	3000	positive	2	5	4.5	3	2	2.5			1	0.98
1	3	1	1	1	2	2	2	584	positive	1	6	5.5	2	1	0.56			1	0.45
3	1	1	1	1	1	1	1	52	positive	1	6	6	1	3	3.747			2	1.46
3	1	1	2	1	2	2	2	2105	positive	1	6	6	1	1	0.88			1	0.56
3	2	1	1	1	2	2	2	1456	positive	2	5.5	6	1	2	2.5			2	1.46
3	2	1	1	1	2	2	2	36.5	positive	2	5	4.5	3	3	4.23			2	2.34
2	1	1	1	1	2	2	2	3000	positive	2	5	5	2	1	0.24	5	4.5	1	0.18
3	1	1	1	1	2	2	2	3000	positive	1	7	6.5	1	1	1.22			1	0.88
1	4	1	1	1	1	1	1	673.4	positive	1	6	6.5	1	4	5.33			3	3.2
1	1	1	1	1	2	2	1	216.6	positive	1	6	6	1	3	3.8			2	1.46

olfar 63	2	32		4.66	5.33	4.54	5	5.25	4.5	1.75	15	11	22		
olfar 64	2	40		4	3	5.71	4	5	5	5	15	19			
olfar 65	2	25		2.66	1	4.57	3.33	3.25	2.75	6	11	16	19		
olfar 66	1	36		3	4.33	4.29	0.66	3	1.75	3.75	15	16	17	24	
olfar 67	2	27		1.33	3.66	4.57	5.66	5.75	2.25	6	15	19			
olfar 68	1	39		3.66	0.33	1.57	2.33	0.5	2.5	3.5					
olfar 69	1	43		4.33	2.33	5	5	4.25	2.5	3.75	11	22	19	11	
olfar 70	2	26		0	0	0.43	1.33	4	2.25	0.25	15	11	16		
olfar 71	2	41		3	3.33	4	4.33	4.75	3.25	5.25	15	16	12		
olfar 72	2	25		0	0.33	1	1.33	0.25	0.5	2	15	2			
olfar 73	1	38		1	0.33	2	4.33	4.5	1	4.5	15	11	16	18	24
olfar 74	1	20		3.33	5	4.86	3.66	4	0.75	3.75	15				
olfar 75	2	40		3.33	3.66	2.14	1.33	2.5	2	4.75	15	22	7		
olfar 76	2	44		1	3.33	1.71	3.83	4.25	2.75	4.5	19	22	6		
olfar 77	1	35		4.33	3	4.29	3.33	3.75	2.5	4	15	11	22		
olfar 78	2	34		5.33	3.33	5.85	6	4.25	4.25	5.5	15	16	4		
olfar 79	2	30		2.33	2.33	4	1.33	3.25	2	3.25	15	11	16	2	
olfar 80	1	18		2	1	1.57	2.66	2.75	1.5	4.5	15	11	16	18	7
olfar 81	2	33		3.33	6	5.14	5.66	4.75	2.75	4.75	15	23	2	13	
olfar 82	1	29		2.66	1	1.85	6	5	2.5	5.5	15	11	12		
olfar 83	1	38		3.33	1.66	4	6	5.5	3.25	5.25	15	11	12		
olfar 84	1	27		4	4	4.57	6	6	2.75	5.5	11	18	23	17	
olfar 85	1	59		4.66	6	4.28	6	4.75	3.75	3.5	15	11	18		
olfar 86	2	23		1.33	3.66	2.14	4.33	4	1.25	3.25	15	13			
olfar 87	1	27		4.33	0.66	1.71	4.66	5	4.5	4.25	15	18	7	6	17
olfar 88	2	45		2	1	1.14	1	2.25	1.25	1	15	11	7		
olfar 89	2	24		5	4.33	2.57	4	2.5	2	3.75	11	16			
olfar 90	1	35		2.66	4.33	3.28	4.33	4.5	4.25	4.25	15	18	13		
olfar 91	2	31		3.33	4.33	3.85	4	3.75	3	4.5	15	11	16		
olfar 92	2	44		3.66	4.66	4.42	3.33	4	4	4.5	15	11	22		
olfar 93	1	31		4.66	4.66	4.14	5	3.5	3.75	4.5	11	12			
olfar 94	2	25		3.33	3.33	2.14	2.33	4.5	4.5	3.75	15	12	19		
olfar 95	1	22		2	0.33	1.14	5	4.5	1.75	2.25	15	11	16	18	
olfar 96	1	32		3	5	4	4.66	4.75	3	4	16	23			
olfar 97	2	60		5.66	2	3.42	5	3.75	4.75	4	15	11			
olfar 98	2	27		5	2	2.14	3.33	5.75	1.75	4.25	15	22	12	2	
olfar 99	2	46		2.66	0	3.42	3.66	4	2.25	4.75	15	11	23	13	
olfar 100	1	21		3.33	0	1.85	5	3.25	1	3	15	11	16	17	
olfar 101	2	59		3.33	0	3.14	5	4.75	1	1.75	15	16			
olfar 102	2	37		4.53	0	3.8	2.75	5.4	1	5.67	15	11	18	12	
olfar 103	1	24		3	2.81	3.14	2.14	1.8	3.5	1.4	15				
olfar 104	1	25									15	11			
olfar 105	1	34									15	11	17	18	12
olfar 106	1	32									15	11	17	4	
olfar 107	1	43									15	11	23		
olfar 108	1	35									11	2	13		
olfar 109	1	42									11	16			
olfar 110	2	24									15				
olfar 111	2	31									18	17			
olfar 112	2	43									11				
olfar 113	2	27									15	18	19	4	
olfar 114	1	36									15	11	16		
olfar 116	1	40									4	5			
olfar 116	2	20									15	16			
olfar 117	1	29									23				
olfar 118	1	43									11	22			
olfar 119	1	39									11	23			
olfar 120	1	32									15	18	22		
olfar 121	2	34									11	22			
olfar 122	1	31									15	11	16	23	13
olfar 123	1	35									15	11	18		
olfar 124	2	31									15	11	12		
olfar 125	1	29									11	15	12		
olfar 126	1	47									11	15			

1	2	1	1	1	1	1	1	462.6	positive	2	4	4.5	2	3	4.43			2	2.62
3	2	1	1	1	1	1	1	59	positive	1	6.5	6	1	4	4.52			2	1.88
3	1	1	1	2	2	2	1	396.3	positive	1	6	6	1	3	3.36			2	2.5
3	2	1	2	1	2	2	1	349.5	positive	1	6	6	1	2	2.97			2	1.84
2	2	1	1	1	1	1	1	349.5	positive	1	6	6	1	3	4.174			3	3.74
1	3	1	1	1	1	1	1	2112	positive	2	3.75	4	2	2	2.055			2	1.32
1	3	1	1	1	1	1	1	437.7	positive	4	3.5	3	4	3	3.88	3	5	1	1.09
3	1	1	1	1	2	2	1	108	positive	1	7	6.5	1	2	1.18			1	0.78
5	2	1	1	1	1	1	1	150.8	positive	1	6	6	1	3	3.99			2	2.65
2	3	1	2	1	2	2	2	740.4	positive	1	6	5.5	2	1	0.77			1	0.54
6	2	1	1	1	1	1	2	1493	positive	1	6	6	1	2	2.52			2	1.82
2	2	1	1	1	1	1	1	148.1	positive	4	2	3	4	3	3.62	5	5	2	1.03
4	4	1	1	1	1	1	1	1028	positive	3	4.5	6	1	2	2.82	5	6	1	0.88
3	3	1	1	1	1	1	1	11.1	positive	2	5.5	6	1	2	2.98			2	1.92
3	2	1	1	1	1	1	1	824.7	positive	2	5	5	2	3	3.6			2	1.24
3	4	1	1	2	1	1	1	689	positive	1	6	6	1	4	4.93			2	1.66
1	2	1	1	1	2	2	1	124	positive	3	3.5	4	2	2	2.64	5	5	1	0.97
2	2	1	1	1	1	1	1	3000	positive	2	4	3.5	3	2	2.31			2	1.54
4	4	1	1	1	1	1	1	485.5	positive	4	2	3	2	4	4.62			2	2.9
3	3	1	1	1	1	1	1	495	positive	3	3	4	2	3	3.5			1	1.18
3	2	1	1	1	1	1	1	653	positive	2	5	5	2	3	4.14			2	2.92
3	2	1	1	1	2	2	1	1070	positive	4	2	2.5	4	4	4.68	3	5	1	1.18
3	2	1	1	2	2	2	1	1088	positive	4	2	2	4	4	4.7	5	5	2	2.82
1	2	1	1	1	1	1	1	150.7	positive	2	4	2	4	2	2.85	5	5	2	1.62
4	3	1	1	1	1	1	2	147.8	positive	3	3	3.5	3	3	3.58				1.65
1	1	1	1	1	1	1	2	383	positive	3	3	4	2	1	1.37				2.3
5	2	1	1	2	1	1	1	276	positive	2	4	4.5	2	3	3.45				0.87
1	3	1	1	1	2	2	1	481	positive	4	2	2	4	3	3.94	5	5		0.92
1	3	1	1	1	1	1	1	620.3	postive	2	4	4.5	2	3	3.82				4.82
3	2	1	1	1	1	1	1	199.8	positive	3	3	4	2	3	4.08	5	6		1.15
3	4	1	1	1	1	1	2	633.4	positive	2	4	4.5	2	3	4.31				1.98
5	2	1	1	1	2	2	1	744.3	positive	2	4.5	4.5	2	3	3.41				0.83
2	1	1	1	1	1	1	1	3000	positive	4	2	2	4	2	2.42	5	5		0.72
6	2	1	1	1	1	1	1	31	positive	1	6	6	1	3	4.05				
1	2	1	1	2	1	1	1	345	positive	2	4.5	3.5	3	3	4.08	6	6		0.93
4	2	1	1	1	1	1	1	3000	postive	2	5	4	2	3	3.46				
2	2	1	1	2	1	1	1	93.4	positive	4	2	2	4	2	2.96	3.5	3		2.98
3	2	1	1	1	1	1	1	1286	positve	4	2	3.5	3	2	2.49				
1	1	1	1	1	2	2	2	36.4	positive	2	4.5	4	2	2	2.71	4	3		
6	2	1	1	1	2	2	1	2311	1	4	2	2	4	3	4.8	3	3		1.21
1	2	1	1	1	2	1	1	1306	1	2	5	5	1	3	4.12				
3	1	1	1	1	2	1	2	560	1	2	4	5	2	2	2.08				
3	2	1	1	1	1	1	2	342.3	1	2	5	6	1	2	2.57				1.22
1	3	1	1	1	1	1	1	916.4	1	2	5	4.5	2	3	3.44				
3	2	1	1	2	1	1	1	2501	1	3	3.5	3	3	2	2.67				1.82
6	1	1	1	1	2	2	1	987	1	3	3.5	3	3	1	1.38				0.96
3	2	2	1	1	1	1	2	960	1	2	4.5	5	2	2	2.77				1.45
6	4	1	1	1	1	1	2	3000	1	2	5	4.5	2	4	5.15				1.51
3	2	1	1	1	1	1	2	133.7	1	4	2	2	4	2	2.79	3	3.5		1.62
3	1	1	1	1	1	1	2	121.7	1	4	2	3.5	3	3	3.76				2.72
1	1	1	1	1	2	2	2	618.7	1	2	5	5	2	2	2.77				1.43
3	2	1	2	1	1	1	1	110	1	2	5	5	2	3	3.84				2.2
1	2	1	1	2	1	1	1	1237	1	4	2	1	5	3	3.68	4	3		2.15
3	1	1	1	2	1	1	2	123	1	2	5	5	2	1	0.66				0.21
2	2	1	1	1	1	1	1	1104	1	2	4.5	5	2	2	2.3				0.32
6	2	1	1	1	1	1	1	104.9	1	2	5	4.5	2	2	2.35				0.81
5	4	1	1	1	1	1	2	345.8	1	2	5	5	2	3	4.09				1.73
1	3	1	1	1	2	1	2	779	1	2	5	5	2	3	3.65				2.74
3	1	1	1	1	1	1	1	223.7	1	2	5	4.5	2	2	1.57				0.63
1	2	1	1	1	1	1	1	110.4	1	2	4.5	5	2	2	2.38				1.9
5	2	1	1	1	1	2	1	504	1	2	5	4.5	2	3	3.9				2.84
6	4	1	1	1	1	2	1	345	1	2	5	4.5	2	2	3.82				1.43
1	1	1	1	2	2	2	2	616.8	1	2	4.5	5	2	1	0.06				0.08

olfar 126	1	47									11	15			
olfar 127	1	21									15	11	16		
olfar 128	2	44									15	11	20	19	
olfar 129	1	20									15	11	16	23	7
olfar 130	1	35									15	18	22		
olfar 131	1	59									15	11	18		
olfar 132	1	50									15	18			
olfar 133	2	44									15	11	16	12	
olfar 134	2	25									15	11	12	23	
olfar 135	1	36									15	11			
olfar 136	1	33									15	11	7		
olfar 137	1	19									15	11	18	22	
olfar 138	2	37									16				
olfar 139	1	50		0.67	0.67	1.34	1.33	2.6	1.25	1.25	15	3			
olfar 140	1	22		2	1.33	1.15	3	3.67	0.75	0.75	11	23			
olfar 141	1	24									11	15	16		
olfar 142	1	50		2	0	3.01	2.67	3.25	2.5	2.25	15	11	22		
olfar 143	1	28									15	2			
olfar 144	2	45									15	16			
olfar 145	2	29									11	18	12	2	
olfar 146	1	31									15	11			
olfar 147	2	35									15	18			
olfar 148	2	40									12				
olfar 149	1	42									15				
olfar 150	1	40		3.67	4.33	4.92	5	3.5	4.25	4.25	15	11	18	12	16

3	2	1	2	1	1	2	1	209.6	1	2	4.5	5	2		2.34				1.56
6	1	2	1	2	1	1	1	3000	1	1	6	6	1		1.89				1.38
3	4	1	1	2	1	1	2	200.1	1	1	6	6	1		4.65				2.13
1	3	1	2	2	1	1	1	3000	1	1	6	6	1		3.82				1.34
5	4	1	2	1	1	1	1	569.9	1	3	3	3.5	3		4.87	4	4		2.15
2	1	1	1	1	1	1	1	125.1	1	1	6	7	1		1.63				0.98
2	1	1	1	1	1	1	1	527.9	1	1	7	6	1		2.98				1.21
3	3	1	1	1	1	1	2	1381	1	1	6	6	1		3.25				1.82
3	1	2	1	1	1	1	2	645.3	1	1	5.5	7	1		1.67				0.93
3	2	1	1	1	1	1	2	406.9	1	3	3.5	3.5	3		2.54				1.63
1	1	1	2	2	1	2	2	254.9	1	1	5.5	6	1		1.82				1.3
5	2	2	1	2	2	2	2	470.7	1	1	6	5.5	1		2.65				1.42
4	3	2	2	1	2	2	2	342	1	3	3	4.5	2		3.12				1.63
4	4	2	1	1	2	2	2	2640	1	1	6	6	1		4.32				1.74
4	2	1	1	1	1	2	2	1422	1	1	6	6	1		2.12				0.92
1	1	1	1	2	1	2	1	310.5	1	1	5.5	5	2		1.98				1.62
3	1	1	1	2	2	2	1	268	1	4	2	2	4		0.87				1.23
5	3	1	1	2	1	2	1	333.2	1	2	4.5	4	2		3.26				2.12
2	2	1	1	2	1	1	1	116.7	1	4	2	2	4		2.74				1.34
5	1	2	1	1	2	1	2	855.5	1	4	2	6	1		1.49				1.24
4	2	2	1	1	2	1	2	233	1	1	6	6	1		3.04				1.87
3	2	2	1	1	1	1	1	120.3	1	1	6	6	1		2.63				1.32
3	1	2	1	1	1	1	2	1430	1	1	6	6	1		1.18				0.97
1	2	1	2	2	1	2	1	11.6	1	2	4	4.5	2		3.45				1.37
1	1	1	1	1	2	2	1	467.3	1	1	6	6	1		0.84				0.68

CONSENT TO TAKE PART IN A CLINICAL TRIAL

Study of olfactory disturbances and quality of life in patients with allergic rhinitis and the reversal of these parameters after medical therapy in affected patients

Study Number:
Participant's name:
Date of Birth / Age (in years):

I_____
_____, son/daughter of _____

(Please tick boxes)
Declare that I have read the information sheet provide to me regarding this study and have clarified any doubts that I had. [ ]
I also understand that my participation in this study is entirely voluntary and that I am free to withdraw permission to continue to participate at any time without affecting my usual treatment or my legal rights [ ]
I also understand that the test will be provided at free of cost
I understand that I will receive free treatment for any study related injury or adverse event but I will not receive and other financial compensation [ ]
I understand that the study staff and institutional ethics committee members will not need my permission to look at my health records even if I withdraw from the trial. I agree to this access [ ]
I understand that my identity will not be revealed in any information released to third parties or published [ ]
I voluntarily agree to take part in this study [ ]

Name:
Signature:
Thumb impression:

Date:

Name of witness:
Relation to participant:

Thumb impression:
Date:

Address of the witness

PROFORMA FOR DATA COLLECTION

Name:
Age :
M/F:
Hospital number:
Phone number:
History- duration

1. Watery nasal discharge Y/N
2. Sneezing Y/N
3. Nasal obstruction Y/N
4. Nasal itching Y/N
5. Watering of eyes Y/N
6. Smoking Y/N

IgE:

Skin Allergy Test:

Butanol Test:

Date of test:
Pre therapy score:
Post therapy score:

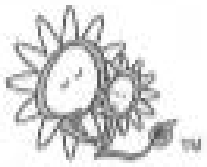
Quality of life:

Pre therapy score:
Post therapy score:

RHINOCONJUNCTIVITIS QUALITY OF LIFE QUESTIONNAIRE WITH STANDARDISED ACTIVITIES (RQLQ(S)

SELF-ADMINISTERED ✓

(≥12 years)



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NOVEMBER 2006

RHINOCONJUNCTIVITIS
QUALITY OF LIFE QUESTIONNAIRE (S)
SELF-ADMINISTERED ≥ 12

PATIENT ID_____

DATE_____

Please complete **all** questions by circling the number that best describes how **troubled** you have been during the **last week as a result of your nose/eye symptoms.**

ACTIVITIES

How **troubled** have you been by each of these activities during the **last week** as a result of your nose/eye symptoms?

	Not troubled	Hardly troubled at all	Somewhat troubled	Moderately troubled	Quite a bit troubled	Very troubled	Extremely troubled
1. REGULAR ACTIVITIES AT HOME AND AT WORK/ SCHOOL (tasks that you have to do regularly at work/school and around your home)	0	1	2	3	4	5	6
2. SOCIAL ACTIVITIES (e.g., activities with your family and friends, playing with children and pets, sex, hobbies)	0	1	2	3	4	5	6
3. OUTDOORS ACTIVITIES (e.g., gardening, mowing the lawn, sitting outdoors, sports, going for a walk)	0	1	2	3	4	5	6

SLEEP

How **troubled** have you been by each of these sleep problems during the **last week** as a result of your nose/eye symptoms?

	Not troubled	Hardly troubled at all	Somewhat troubled	Moderately troubled	Quite a bit troubled	Very troubled	Extremely troubled
4. Difficulty getting to sleep	0	1	2	3	4	5	6
5. Wake up during night	0	1	2	3	4	5	6
6. Lack of a good night's sleep	0	1	2	3	4	5	6

RHINOCONJUNCTIVITIS
QUALITY OF LIFE QUESTIONNAIRE (S)
SELF-ADMINISTERED ≥ 12

PATIENT ID_____

DATE_____

NON-NOSE/EYE SYMPTOMS

How **troubled** have you been during the **last week** as a result of these symptoms?

		Not troubled	Hardly troubled at all	Somewhat troubled	Moderately troubled	Quite a bit troubled	Very troubled	Extremely troubled
7.	Fatigue	0	1	2	3	4	5	6
8.	Thirst	0	1	2	3	4	5	6
9.	Reduced productivity	0	1	2	3	4	5	6
10.	Tiredness	0	1	2	3	4	5	6
11.	Poor concentration	0	1	2	3	4	5	6
12.	Headache	0	1	2	3	4	5	6
13.	Worn out	0	1	2	3	4	5	6

PRACTICAL PROBLEMS

How **troubled** have you been by each of these problems during the **last week** as a result of your nose/eye symptoms?

		Not troubled	Hardly troubled at all	Somewhat troubled	Moderately troubled	Quite a bit troubled	Very troubled	Extremely troubled
14.	Inconvenience of having to carry tissues or handkerchief	0	1	2	3	4	5	6
15.	Need to rub nose/eyes	0	1	2	3	4	5	6
16.	Need to blow nose repeatedly	0	1	2	3	4	5	6

NASAL SYMPTOMS

How **troubled** have you been by each of these symptoms during the **last week**?

	Not troubled	Hardly troubled at all	Somewhat troubled	Moderately troubled	Quite a bit troubled	Very troubled	Extremely troubled
17. Stuffy/blocked	0	1	2	3	4	5	6
18. Runny	0	1	2	3	4	5	6
19. Sneezing	0	1	2	3	4	5	6
20. Post nasal drip	0	1	2	3	4	5	6

EYE SYMPTOMS

How **troubled** have you been by each of these symptoms during the **last week**?

	Not troubled	Hardly troubled at all	Somewhat troubled	Moderately troubled	Quite a bit troubled	Very troubled	Extremely troubled
21. Itchy eyes	0	1	2	3	4	5	6
22. Watery eyes	0	1	2	3	4	5	6
23. Sore eyes	0	1	2	3	4	5	6
24. Swollen eyes	0	1	2	3	4	5	6

EMOTIONAL

How often during the **last week** have you been troubled by these emotions as a result of your nose/eye symptoms?

	None of the time	Hardly any time at all	A small part of the time	Some of the time	A good part of the time	Most of the time	All of the time
25. Frustrated	0	1	2	3	4	5	6
26. Impatient or restless	0	1	2	3	4	5	6
27. Irritable	0	1	2	3	4	5	6
28. Embarrassed by your symptoms	0	1	2	3	4	5	6